ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Violet white, ovaloid convex film-coated tablet with bevelled edges, with "YIY" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology
The recommended dose of Rasitrio is one tablet per day.

Patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets given concurrently at the same time of the day may be switched to a fixed combination tablet of Rasitrio containing the same component doses.

The fixed dose combination should only be used after a stable effect on the monocomponents, given concurrently, has been established after dose titration. Dose should be individualised and adjusted according to the patient's clinical response.

Special populations
Elderly patients aged 65 years and over
There is evidence of an increased risk of adverse events related to hypotension in patients aged 65 years or older treated with Rasitrio. Therefore, particular caution should be exercised when administering Rasitrio in patients aged 65 years or over.

The recommended starting dose of aliskiren in this group of patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Elderly patients aged 75 years and over
Very limited data are available on the use of Rasitrio in patients aged 75 years or older (see section 5.2). The use of Rasitrio in patients aged 75 years or older should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.4, 4.8, 5.1 and 5.2).

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate (GFR) 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively) (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Rasitrio is contraindicated for use in patients with anuria and in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2). The concomitant use of Rasitrio with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Rasitrio in patients with mild to moderate hepatic impairment or patients with progressive liver disease. No dosage recommendations have been established for amlodipine in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasitrio should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasitrio (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to other dihydropyridine derivatives, or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2).
- Hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia and refractory hypokalaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

General
In the event of severe and persistent diarrhoea, Rasitrio therapy should be stopped (see section 4.8).

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended. Close monitoring of blood pressure, renal function and electrolytes should be exercised if co-administration is considered absolutely necessary.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

Geriatric patients aged 65 years and over
Particular caution should be exercised when administering Rasitrio in patients aged 65 years or older. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Patients aged 65 years old or over, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2).

Geriatric patients aged 75 years and over
Very limited efficacy and safety data are available on the use of Rasitrio in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.2, 4.8, 5.1 and 5.2).

Heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

No data on cardiovascular mortality and morbidity are available for Rasitrio in patients with heart failure (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasitrio in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or
- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasitrio, or the treatment should start under close medical supervision.

Electrolyte imbalance

Treatment with Rasitrio should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy Rasitrio should be discontinued until stable correction of the potassium balance.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3, 4.5 and 4.8).

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Rasitrio therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

There is no evidence that Rasitrio would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Renal impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasitrio is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. No data is available in hypertensive patients with severe renal impairment (serum creatinine ≥150 µmol/l or 1.70 mg/dl in women and ≥177 µmol/l or 2.00 mg/dl in men and/or estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Rasitrio is contraindicated in hypertensive patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) or anuria (see sections 4.2. and 4.3). No dose adjustment is necessary in patients with mild to moderate renal impairment.

As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients.

Hepatic impairment
Rasitrio is contraindicated in hypertensive patients with severe hepatic impairment (see sections 4.3 and 5.2). Caution should be exercised when administering Rasitrio to patients with mild to moderate hepatic impairment or progressive liver disease (see sections 4.2 and 5.2).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dose adjustments of insulin or oral hypoglycaemic medicinal products may be required during Rasitrio therapy. Concomitant use of Rasitrio with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Rasitrio is contraindicated in symptomatic hyperuricaemia (see section 4.3). Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis
No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema
Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). As with other medicinal products acting on the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal products that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, Rasitrio should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasitrio, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of treatment initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasitrio interactions
A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) and C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocoricotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Rasitrio is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Rasitrio with an NSAID requires caution, especially in elderly patients.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *Dual RAAS blockade*

The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *P-glycoprotein (P-gp) potent inhibitors*

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended (see section 4.2)
- *Grapefruit juice*

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio.

Caution required with concomitant use

- *P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

- *Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

- *Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

- *Food interactions*

Meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially (see section 4.2).

No interactions

- Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

- Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. Co-administration of aliskiren had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

- Digoxin and verapamil bioavailability may be slightly decreased by aliskiren.

- *CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

- *P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

- *Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

- *CYP3A4 inducers*

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

- *Grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

- *Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

- The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other antihypertensive medicinal products.

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

No interactions

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Information on hydrochlorothiazide interactions

When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Not recommended

- *Lithium*

Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Caution required with concomitant use

- *Alcohol, barbiturates or narcotics*

Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

- *Amantadine*

Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

- *Antidiabetic agents (e.g. insulin and oral antidiabetic agents)*

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

- *Anticholinergic agents and other medicinal products affecting gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.

- *Medicinal products used in the treatment of gout*

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

- *Medicinal products that could induce torsades de pointes*

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

- *Medicinal products affecting serum sodium level*

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

- *Beta blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

- *Ion exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

- *Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy, or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

- *Non-depolarising skeletal muscle relaxants*

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

- *Cytotoxic agents*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

- *Digoxine or digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

- *Methyldopa*

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

- *Iodine contrasting agents*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

- *Pressor amines (e.g. noradrenaline, adrenaline)*

Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant.

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the renin-angiotensin-aldosterone system have been associated with serious foetal malformations and neonatal death. As for any medicinal product that acts directly on the renin-angiotensin-aldosterone system, aliskiren should not be used during the first trimester of pregnancy and is contraindicated during the second and third trimesters (see section 4.3).

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3).

If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible.

Breast-feeding

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Rasitrio during breast-feeding is not recommended. If Rasitrio is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility with the use of Rasitrio.

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3). The fertility of rats was unaffected at doses of up to aliskiren 250 mg/kg/day and hydrochlorothiazide 4 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, drowsiness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

Aliskiren/amlodipine/hydrochlorothiazide combination
The safety profile of Rasitrio presented below is based on clinical studies performed with Rasitrio and the known safety profile of the individual components aliskiren, amlodipine and hydrochlorothiazide. Safety information for Rasitrio in patients aged 75 years and older is limited.

The most frequent adverse reactions observed with Rasitrio are hypotension and dizziness. The adverse reactions previously reported with one of the individual components of Rasitrio (aliskiren, amlodipine and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Rasitrio.

Tabulated list of adverse reactions:
The adverse reactions for aliskiren, amlodipine and hydrochlorothiazide are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Information on Rasitrio

Nervous system disorders	
Common	Dizziness
Vascular disorders	
Common	Hypotension
General disorders and administration site conditions	
Common	Peripheral oedema

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The incidence of peripheral oedema for Rasitrio in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

The incidence of any adverse reactions potentially related to hypotension in a short-term active controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Rasitrio even if not observed in clinical trials.

Aliskiren
Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:
The known aliskiren adverse reactions are presented in the table below using the same convention as described previously for the fixed combination.

Immune system disorders		
	Rare	Anaphylactic reactions, hypersensitivity reactions
Cardiac disorders		
	Common	Dizziness
	Uncommon	Palpitations, oedema peripheral
Vascular disorders		
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Cough
Gastrointestinal disorders		
	Common	Diarrhoea
Hepatobiliary disorders		
	Not known	Liver disorder*, jaundice, hepatitis, liver failure**
Skin and subcutaneous tissue disorders		
	Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN), oral mucosal reactions, rash, pruritus, urticaria
	Rare	Angioedema, erythema
Musculoskeletal and connective tissue disorders		
	Common	Arthralgia
Renal and urinary disorders		
	Uncommon	Acute renal failure, renal impairment
Investigations		
	Common	Hyperkalaemia
	Uncommon	Liver enzyme increased
	Rare	Haemoglobin decreased, haematocrit decreased, blood creatinine increased

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.
**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse events:
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicinal products known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing, or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

Investigations: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other medicinal products acting on the RAAS, such as ACEIs and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Paediatric population: Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.

Amlodipine

Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes (including anxiety), depression
Rare	Confusion
Nervous system disorders	
Common	Somnolence, headache (especially at the beginning of treatment)
Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Eye disorders	
Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	
Common	Flushing
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, purpura, skin decolouration, hyperhidrosis, pruritus, rash, exanthema
Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Ankle swelling
Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Chest pain, asthenia, pain, malaise
Investigations	
Uncommon	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasitrio. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare	Thrombocytopenia sometimes with purpura
	Very rare	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known	Aplastic anaemia
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Hypokalaemia
	Common	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare	Depression, sleep disturbances
Nervous system disorders		
	Rare	Dizziness, headache, paraesthesia
Eye disorders		
	Rare	Visual impairment
	Not known	Acute angle-closure glaucoma
Cardiac disorders		
	Rare	Cardiac arrhythmias
Vascular disorders		
	Common	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common	Decreased appetite, mild nausea and vomiting
	Rare	Abdominal discomfort, constipation, diarrhoea
	Very rare	Pancreatitis
Hepatobiliary disorders		
	Rare	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common	Urticaria and other forms of rash
	Rare	Photosensitivity reactions
	Very rare	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known	Muscle spasm
Renal and urinary disorders		
	Not known	Renal dysfunction, acute renal failure
Reproductive system and breast disorders		
	Common	Impotence

General disorders and administration site conditions	
Not known	Asthenia, pyrexia
Investigations	
Very common	Increases in cholesterol and triglycerides
Rare	Glycosuria

4.9 Overdose

Symptoms
The most likely manifestation of overdose for Rasitrio would be hypotension, related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

With aliskiren, the most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

With amlodipine, available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome, have been reported with amlodipine.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products.

Treatment
If symptomatic hypotension should occur with Rasitrio, supportive treatment should be initiated.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin-inhibitors; ATC code C09XA54

Rasitrio combines three antihypertensive active substances with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine to the calcium channel blocker class and hydrochlorothiazide to the thiazide diuretics class. When combined, the consolidated effects of inhibition of the renin-angiotensin-aldosterone system, calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combinations.

Aliskiren/amlodipine/hydrochlorothiazide combination
In hypertensive patients, once-daily administration of Rasitrio provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for Rasitrio over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

Rasitrio was studied in a double-blind, randomised, active-controlled study in 1,181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP >180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes. During the first 4 weeks of double-blind treatment, patients received triple combination aliskiren/amlodipine/hydrochlorothiazide (HCTZ) 150/5/12.5 mg (N=308), or dual combinations of aliskiren/HCTZ 150/12.5 mg (N=295), aliskiren/amlodipine 150/5 mg (N=282) and amlodipine/HCTZ 5/12.5 mg (N=295). Patients were force-titrated to higher doses after 4 weeks for an additional 4 weeks of double-blind treatment to aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg and amlodipine/HCTZ 10/25 mg.

In this study, Rasitrio at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥180 mmHg), the reduction in blood pressure from baseline for Rasitrio and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). In a subset of 588 patients in which patients >65 years were scarcely represented and those aged >75 years were very scarcely represented, the combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) produced a systolic/diastolic mean blood pressure reduction of 39.7/21.1 mmHg from baseline, compared to 31.3/18.74 mmHg for aliskiren/amlodipine (300/10 mg), 25.5/12.5 mmHg for aliskiren/hydrochlorothiazide (300/25 mg) and 29.2/16.4 mmHg for amlodipine/hydrochlorothiazide (10/25 mg) (the subset constitutes patients without aberrant readings, defined as a difference between systolic blood pressure (SBP) readings ≥10 mmHg at baseline or endpoint). The effect of Rasitrio was observed as early as one week after initiation of therapy. The blood-pressure-lowering effect in patients with moderate to severe hypertension was independent of age, gender, race, body mass index and overweight-associated disorders (metabolic syndrome and diabetes).

Rasitrio was associated with a significant reduction in plasma renin activity (PRA) (-34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA (+170%). The clinical implications of the differences in effect on PRA are not known at the present time.

In a 28 to 54 week open label safety study, efficacy was measured as secondary endpoint and Rasitrio at a dose of 300/10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of Rasitrio was maintained over one year of treatment, with no evidence of loss of effect.

In a randomised, double blind, active controlled, 36-week study in elderly patients whose blood pressure was not controlled with aliskiren/HCTZ 300/25 mg (SBP ≥140 mmHg), clinically meaningful further BP reduction was seen at week 36 endpoint for patients who received Rasitrio at a dose of 300/10/25 mg (from reductions in msSBP/msDBP of 15.0/8.6 mmHg at week 22 to reductions of 30.8/14.1 mmHg at week 36 endpoint).

Rasitrio has been administered to more than 1,155 patients in completed clinical trials, including 182 patients for one year or more. Treatment with Rasitrio was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar to the corresponding dual combinations, except for symptomatic hypotension. The incidence of any adverse reactions potentially related to hypotension in a short-term controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

The incidence of adverse events did not show any association with gender, age (with the exception of symptomatic hypotension), body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Very limited safety data are available for patients aged >75 years or patients with major cardiovascular co-morbidities. Discontinuation of therapy due to a clinical adverse event occurred in 3.6% of patients treated with Rasitrio versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other medicinal products that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive medicinal products. The clinical implications of the differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood-pressure-lowering effects comparable to other classes of antihypertensive medicinal products including selected ACEI and ARB. Compared to a diuretic (hydrochlorothiazide, HCTZ), aliskiren 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Aliskiren induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12-week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In an 8-week study in 754 hypertensive geriatric patients aged 65 years or older and geriatric patients aged 75 years or older (30%) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive medicinal products. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR <60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Study results indicated a hazard ratio for the primary endpoint of 1.11 in favour of placebo (95% Confidence Interval: 1.00, 1.23, 2-sided p=0.05). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (37.9% versus 30.2%). In particular there was an increased incidence of renal dysfunction (14.0% versus 12.1%), hyperkalaemia (38.9% versus 28.8%), hypotension-related events (19.7% versus 16.2%) and adjudicated stroke endpoints (3.4% versus 2.6%). The increased incidence of stroke was greater in patients with renal insufficiency.

Effects of aliskiren on mortality and cardiovascular morbidity are currently unknown.

No long-term efficacy data for aliskiren in patients with heart failure are currently available (see section 4.4).

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Amlodipine
The amlodipine component of Rasitrio inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Use in patients with heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasitrio in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Aliskiren/amlodipine/hydrochlorothiazide combination
Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Aliskiren
Absorption
Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and AUC $_{0-tau}$ by 67% in hypertensive patients. Steady-state plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution
Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation and elimination
The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients (aged 6-17 years) given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The available data did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

<u>Amlodipine</u>
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
The volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days.

Linearity
Amlodipine exhibits linear pharmacokinetics between the therapeutic dose range of 5 mg and 10 mg.

<u>Hydrochlorothiazide</u>
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Linearity
The increase in mean AUC is linear and dose proportional in the therapeutic range.

Special populations
Rasitrio is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

Renal impairment
Due to its hydrochlorothiazide component, Rasitrio is contraindicated in patients with anuria or severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.3). No adjustment of the initial dose is required in patients with mild to moderate renal impairment (see sections 4.4 and 4.2).

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dose of aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2). Concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment (see section 4.3).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to moderate hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised in patients with hepatic impairment.

Geriatric patients
No data are available on systemic exposure after administration of Rasitrio in geriatric patients. When administered alone, the AUC of aliskiren in geriatric subjects (>65 years) is 50% higher than in young subjects. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in geriatric patients. Therefore particular caution is recommended when administering Rasitrio to patients aged 65 years and over, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. There are no specific data regarding the effect of hydrochlorothiazide in elderly patients.

Paediatric population (age below 18 years)
The pharmacokinetics of Rasitrio have not been investigated. A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

5.3 Preclinical safety data

Aliskiren/hydrochlorothiazide and aliskiren/amlodipine
Non-clinical studies of the toxicology of Rasitrio alone have not been conducted as these studies have been conducted for the individual components.

The toxicity profiles of the combination of aliskiren/hydrochlorothiazide and aliskiren/amlodipine have been well characterised in preclinical studies. Both combinations were generally well tolerated by rats. The findings from 2- and 13-week oral toxicity studies were consistent with those for the individual components.

Aliskiren
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren.

Amlodipine
Safety data for amlodipine are well established both clinically and non-clinically.

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no effects related to the medicinal product at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Hydrochlorothiazide
Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg,/day respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/polychlorotrifluoroethylene (PCTFE) – Alu calendar blisters:
2 years

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
2 years

PA/Alu/PVC – Alu calendar blisters:
18 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets

PVC/polychlorotrifluoroethylene (PCTFE) - Alu blisters:
Single pack containing 30, 90 tablets
Unit dose pack (perforated unit dose blister) containing 56x1 tablet
Multipacks of unit dose (perforated unit dose blister) containing 98x1 tablet (2 packs of 49x1)

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multipacks containing 98 tablets (2 packs of 49)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light pink, ovaloid convex film-coated tablet with bevelled edges, with “LIL” debossed on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology
The recommended dose of Rasitrio is one tablet per day.

Patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets given concurrently at the same time of the day may be switched to a fixed combination tablet of Rasitrio containing the same component doses.

The fixed dose combination should only be used after a stable effect on the monocomponents, given concurrently, has been established after dose titration. Dose should be individualised and adjusted according to the patient’s clinical response.

Special populations
Elderly patients aged 65 years and over
There is evidence of an increased risk of adverse events related to hypotension in patients aged 65 years or older treated with Rasitrio. Therefore, particular caution should be exercised when administering Rasitrio in patients aged 65 years or over.

The recommended starting dose of aliskiren in this group of patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Elderly patients aged 75 years and over
Very limited data are available on the use of Rasitrio in patients aged 75 years or older (see section 5.2). The use of Rasitrio in patients aged 75 years or older should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.4, 4.8, 5.1 and 5.2).

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate (GFR) 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively) (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Rasitrio is contraindicated for use in patients with anuria and in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2). The concomitant use of Rasitrio with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Rasitrio in patients with mild to moderate hepatic impairment or patients with progressive liver disease. No dosage recommendations have been established for amlodipine in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasitrio should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasitrio (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to other dihydropyridine derivatives, or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2).
- Hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia and refractory hypokalaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

General
In the event of severe and persistent diarrhoea, Rasitrio therapy should be stopped (see section 4.8).

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended. Close monitoring of blood pressure, renal function and electrolytes should be exercised if co-administration is considered absolutely necessary.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

Geriatric patients aged 65 years and over
Particular caution should be exercised when administering Rasitrio in patients aged 65 years or older. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Patients aged 65 years old or over, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2).

Geriatric patients aged 75 years and over
Very limited efficacy and safety data are available on the use of Rasitrio in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.2, 4.8, 5.1 and 5.2).

Heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

No data on cardiovascular mortality and morbidity are available for Rasitrio in patients with heart failure (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasitrio in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or
- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasitrio, or the treatment should start under close medical supervision.

Electrolyte imbalance

Treatment with Rasitrio should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy Rasitrio should be discontinued until stable correction of the potassium balance.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3, 4.5 and 4.8).

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Rasitrio therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

There is no evidence that Rasitrio would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Renal impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasitrio is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. No data is available in hypertensive patients with severe renal impairment (serum creatinine ≥150 µmol/l or 1.70 mg/dl in women and ≥177 µmol/l or 2.00 mg/dl in men and/or estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Rasitrio is contraindicated in hypertensive patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) or anuria (see sections 4.2. and 4.3). No dose adjustment is necessary in patients with mild to moderate renal impairment.

As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients.

Hepatic impairment
Rasitrio is contraindicated in hypertensive patients with severe hepatic impairment (see sections 4.3 and 5.2). Caution should be exercised when administering Rasitrio to patients with mild to moderate hepatic impairment or progressive liver disease (see sections 4.2 and 5.2).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dose adjustments of insulin or oral hypoglycaemic medicinal products may be required during Rasitrio therapy. Concomitant use of Rasitrio with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Rasitrio is contraindicated in symptomatic hyperuricaemia (see section 4.3). Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis
No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema
Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). As with other medicinal products acting on the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal products that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, Rasitrio should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasitrio, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of treatment initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasitrio interactions
A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) and C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocoricotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Rasitrio is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Rasitrio with an NSAID requires caution, especially in elderly patients.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *Dual RAAS blockade*

The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *P-glycoprotein (P-gp) potent inhibitors*

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended (see section 4.2)
- *Grapefruit juice*

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio.

Caution required with concomitant use

- *P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

- *Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

- *Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

- *Food interactions*

Meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially (see section 4.2).

No interactions

- Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

- Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. Co-administration of aliskiren had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

- Digoxin and verapamil bioavailability may be slightly decreased by aliskiren.

- *CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

- *P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

- *Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

- *CYP3A4 inducers*

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

- *Grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

- *Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

- The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other antihypertensive medicinal products.

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

No interactions

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Information on hydrochlorothiazide interactions

When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Not recommended

- *Lithium*

Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Caution required with concomitant use

- *Alcohol, barbiturates or narcotics*

Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

- *Amantadine*

Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

- *Antidiabetic agents (e.g. insulin and oral antidiabetic agents)*

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

- *Anticholinergic agents and other medicinal products affecting gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.

- *Medicinal products used in the treatment of gout*

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

- *Medicinal products that could induce torsades de pointes*

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

- *Medicinal products affecting serum sodium level*

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

- *Beta blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

- *Ion exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

- *Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy, or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

- *Non-depolarising skeletal muscle relaxants*

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

- *Cytotoxic agents*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

- *Digoxine or digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

- *Methyldopa*

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

- *Iodine contrasting agents*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

- *Pressor amines (e.g. noradrenaline, adrenaline)*

Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant.

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the renin-angiotensin-aldosterone system have been associated with serious foetal malformations and neonatal death. As for any medicinal product that acts directly on the renin-angiotensin-aldosterone system, aliskiren should not be used during the first trimester of pregnancy and is contraindicated during the second and third trimesters (see section 4.3).

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3).

If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible.

Breast-feeding

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Rasitrio during breast-feeding is not recommended. If Rasitrio is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility with the use of Rasitrio.

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3). The fertility of rats was unaffected at doses of up to aliskiren 250 mg/kg/day and hydrochlorothiazide 4 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, drowsiness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

Aliskiren/amlodipine/hydrochlorothiazide combination
The safety profile of Rasitrio presented below is based on clinical studies performed with Rasitrio and the known safety profile of the individual components aliskiren, amlodipine and hydrochlorothiazide. Safety information for Rasitrio in patients aged 75 years and older is limited.

The most frequent adverse reactions observed with Rasitrio are hypotension and dizziness. The adverse reactions previously reported with one of the individual components of Rasitrio (aliskiren, amlodipine and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Rasitrio.

Tabulated list of adverse reactions:
The adverse reactions for aliskiren, amlodipine and hydrochlorothiazide are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Information on Rasitrio

Nervous system disorders	
Common	Dizziness
Vascular disorders	
Common	Hypotension
General disorders and administration site conditions	
Common	Peripheral oedema

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The incidence of peripheral oedema for Rasitrio in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

The incidence of any adverse reactions potentially related to hypotension in a short-term active controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Rasitrio even if not observed in clinical trials.

Aliskiren
Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:
The known aliskiren adverse reactions are presented in the table below using the same convention as described previously for the fixed combination.

Immune system disorders		
	Rare	Anaphylactic reactions, hypersensitivity reactions
Cardiac disorders		
	Common	Dizziness
	Uncommon	Palpitations, oedema peripheral
Vascular disorders		
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Cough
Gastrointestinal disorders		
	Common	Diarrhoea
Hepatobiliary disorders		
	Not known	Liver disorder*, jaundice, hepatitis, liver failure**
Skin and subcutaneous tissue disorders		
	Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN), oral mucosal reactions, rash, pruritus, urticaria
	Rare	Angioedema, erythema
Musculoskeletal and connective tissue disorders		
	Common	Arthralgia
Renal and urinary disorders		
	Uncommon	Acute renal failure, renal impairment
Investigations		
	Common	Hyperkalaemia
	Uncommon	Liver enzyme increased
	Rare	Haemoglobin decreased, haematocrit decreased, blood creatinine increased

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.
**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse events:
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicinal products known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing, or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

Investigations: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other medicinal products acting on the RAAS, such as ACEIs and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Paediatric population: Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.

Amlodipine

Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes (including anxiety), depression
Rare	Confusion
Nervous system disorders	
Common	Somnolence, headache (especially at the beginning of treatment)
Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Eye disorders	
Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	
Common	Flushing
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, purpura, skin decolouration, hyperhidrosis, pruritus, rash, exanthema
Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Ankle swelling
Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Chest pain, asthenia, pain, malaise
Investigations	
Uncommon	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasitrio. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare	Thrombocytopenia sometimes with purpura
	Very rare	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known	Aplastic anaemia
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Hypokalaemia
	Common	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare	Depression, sleep disturbances
Nervous system disorders		
	Rare	Dizziness, headache, paraesthesia
Eye disorders		
	Rare	Visual impairment
	Not known	Acute angle-closure glaucoma
Cardiac disorders		
	Rare	Cardiac arrhythmias
Vascular disorders		
	Common	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common	Decreased appetite, mild nausea and vomiting
	Rare	Abdominal discomfort, constipation, diarrhoea
	Very rare	Pancreatitis
Hepatobiliary disorders		
	Rare	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common	Urticaria and other forms of rash
	Rare	Photosensitivity reactions
	Very rare	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known	Muscle spasm
Renal and urinary disorders		
	Not known	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common	Impotence
General disorders and administration site conditions		
	Not known	Asthenia, pyrexia
Investigations		
	Very common	Increases in cholesterol and triglycerides
	Rare	Glycosuria

4.9 Overdose

Symptoms
The most likely manifestation of overdose for Rasitrio would be hypotension, related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

With aliskiren, the most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

With amlodipine, available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome, have been reported with amlodipine.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products.

Treatment
If symptomatic hypotension should occur with Rasitrio, supportive treatment should be initiated.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin-inhibitors; ATC code C09XA54

Rasitrio combines three antihypertensive active substances with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine to the calcium channel blocker class and hydrochlorothiazide to the thiazide diuretics class. When combined, the consolidated effects of inhibition of the renin-angiotensin-aldosterone system, calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combinations.

Aliskiren/amlodipine/hydrochlorothiazide combination
In hypertensive patients, once-daily administration of Rasitrio provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for Rasitrio over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

Rasitrio was studied in a double-blind, randomised, active-controlled study in 1,181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP >180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes. During the first 4 weeks of double-blind treatment, patients received triple combination aliskiren/amlodipine/hydrochlorothiazide (HCTZ) 150/5/12.5 mg (N=308), or dual combinations of aliskiren/HCTZ 150/12.5 mg (N=295), aliskiren/amlodipine 150/5 mg (N=282) and amlodipine/HCTZ 5/12.5 mg (N=295). Patients were force-titrated to higher doses after 4 weeks for an additional 4 weeks of double-blind treatment to aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg and amlodipine/HCTZ 10/25 mg.

In this study, Rasitrio at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥180 mmHg), the reduction in blood pressure from baseline for Rasitrio and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). In a subset of 588 patients in which patients >65 years were scarcely represented and those aged >75 years were very scarcely represented, the combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) produced a systolic/diastolic mean blood pressure reduction of 39.7/21.1 mmHg from baseline, compared to 31.3/18.74 mmHg for aliskiren/amlodipine (300/10 mg), 25.5/12.5 mmHg for aliskiren/hydrochlorothiazide (300/25 mg) and 29.2/16.4 mmHg for amlodipine/hydrochlorothiazide (10/25 mg) (the subset constitutes patients without aberrant readings, defined as a difference between systolic blood pressure (SBP) readings ≥10 mmHg at baseline or endpoint). The effect of Rasitrio was observed as early as one week after initiation of therapy. The blood-pressure-lowering effect in patients with moderate to severe hypertension was independent of age, gender, race, body mass index and overweight-associated disorders (metabolic syndrome and diabetes).

Rasitrio was associated with a significant reduction in plasma renin activity (PRA) (-34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA (+170%). The clinical implications of the differences in effect on PRA are not known at the present time.

In a 28 to 54 week open label safety study, efficacy was measured as secondary endpoint and Rasitrio at a dose of 300/10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of Rasitrio was maintained over one year of treatment, with no evidence of loss of effect.

In a randomised, double blind, active controlled, 36-week study in elderly patients whose blood pressure was not controlled with aliskiren/HCTZ 300/25 mg (SBP ≥140 mmHg), clinically meaningful further BP reduction was seen at week 36 endpoint for patients who received Rasitrio at a dose of 300/10/25 mg (from reductions in msSBP/msDBP of 15.0/8.6 mmHg at week 22 to reductions of 30.8/14.1 mmHg at week 36 endpoint).

Rasitrio has been administered to more than 1,155 patients in completed clinical trials, including 182 patients for one year or more. Treatment with Rasitrio was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar to the corresponding dual combinations, except for symptomatic hypotension. The incidence of any adverse reactions potentially related to hypotension in a short-term controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

The incidence of adverse events did not show any association with gender, age (with the exception of symptomatic hypotension), body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Very limited safety data are available for patients aged >75 years or patients with major cardiovascular co-morbidities. Discontinuation of therapy due to a clinical adverse event occurred in 3.6% of patients treated with Rasitrio versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other medicinal products that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive medicinal products. The clinical implications of the differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood-pressure-lowering effects comparable to other classes of antihypertensive medicinal products including selected ACEI and ARB. Compared to a diuretic (hydrochlorothiazide, HCTZ), aliskiren 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Aliskiren induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12-week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In an 8-week study in 754 hypertensive geriatric patients aged 65 years or older and geriatric patients aged 75 years or older (30%) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive medicinal products. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR <60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Study results indicated a hazard ratio for the primary endpoint of 1.11 in favour of placebo (95% Confidence Interval: 1.00, 1.23, 2-sided p=0.05). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (37.9% versus 30.2%). In particular there was an increased incidence of renal dysfunction (14.0% versus 12.1%), hyperkalaemia (38.9% versus 28.8%), hypotension-related events (19.7% versus 16.2%) and adjudicated stroke endpoints (3.4% versus 2.6%). The increased incidence of stroke was greater in patients with renal insufficiency.

Effects of aliskiren on mortality and cardiovascular morbidity are currently unknown.

No long-term efficacy data for aliskiren in patients with heart failure are currently available (see section 4.4).

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Amlodipine
The amlodipine component of Rasitrio inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Use in patients with heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasitrio in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Aliskiren/amlodipine/hydrochlorothiazide combination
Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Aliskiren
Absorption
Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and AUC $_{0\text{-}tau}$ by 67% in hypertensive patients. Steady-state plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution
Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation and elimination
The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients (aged 6-17 years) given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The available data did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

<u>Amlodipine</u>
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
The volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days.

Linearity
Amlodipine exhibits linear pharmacokinetics between the therapeutic dose range of 5 mg and 10 mg.

<u>Hydrochlorothiazide</u>
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Linearity
The increase in mean AUC is linear and dose proportional in the therapeutic range.

Special populations
Rasitrio is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

Renal impairment
Due to its hydrochlorothiazide component, Rasitrio is contraindicated in patients with anuria or severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.3). No adjustment of the initial dose is required in patients with mild to moderate renal impairment (see sections 4.4 and 4.2).

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dose of aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2). Concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment (see section 4.3).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to moderate hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised in patients with hepatic impairment.

Geriatric patients
No data are available on systemic exposure after administration of Rasitrio in geriatric patients. When administered alone, the AUC of aliskiren in geriatric subjects (>65 years) is 50% higher than in young subjects. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in geriatric patients. Therefore particular caution is recommended when administering Rasitrio to patients aged 65 years and over, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. There are no specific data regarding the effect of hydrochlorothiazide in elderly patients.

Paediatric population (age below 18 years)
The pharmacokinetics of Rasitrio have not been investigated. A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

5.3 Preclinical safety data

Aliskiren/hydrochlorothiazide and aliskiren/amlodipine
Non-clinical studies of the toxicology of Rasitrio alone have not been conducted as these studies have been conducted for the individual components.

The toxicity profiles of the combination of aliskiren/hydrochlorothiazide and aliskiren/amlodipine have been well characterised in preclinical studies. Both combinations were generally well tolerated by rats. The findings from 2- and 13-week oral toxicity studies were consistent with those for the individual components.

Aliskiren
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically.

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no effects related to the medicinal product at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Hydrochlorothiazide

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg,/day respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/polychlorotrifluoroethylene (PCTFE) – Alu calendar blisters:
2 years

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
2 years

PA/Alu/PVC – Alu calendar blisters:
18 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets

PVC/polychlorotrifluoroethylene (PCTFE) - Alu blisters:
Single pack containing 30, 90 tablets
Unit dose pack (perforated unit dose blister) containing 56x1 tablet
Multipacks of unit dose (perforated unit dose blister) containing 98x1 tablet (2 packs of 49x1)

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multipacks containing 98 tablets (2 packs of 49)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/013-024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 25 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale orange-brown, ovaloid convex film-coated tablet with bevelled edges, with "NVR" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology
The recommended dose of Rasitrio is one tablet per day.

Patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets given concurrently at the same time of the day may be switched to a fixed combination tablet of Rasitrio containing the same component doses.

The fixed dose combination should only be used after a stable effect on the monocomponents, given concurrently, has been established after dose titration. Dose should be individualised and adjusted according to the patient's clinical response.

Special populations
Elderly patients aged 65 years and over
There is evidence of an increased risk of adverse events related to hypotension in patients aged 65 years or older treated with Rasitrio. Therefore, particular caution should be exercised when administering Rasitrio in patients aged 65 years or over.

The recommended starting dose of aliskiren in this group of patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Elderly patients aged 75 years and over
Very limited data are available on the use of Rasitrio in patients aged 75 years or older (see section 5.2). The use of Rasitrio in patients aged 75 years or older should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.4, 4.8, 5.1 and 5.2).

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate (GFR) 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively) (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Rasitrio is contraindicated for use in patients with anuria and in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2). The concomitant use of Rasitrio with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Rasitrio in patients with mild to moderate hepatic impairment or patients with progressive liver disease. No dosage recommendations have been established for amlodipine in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasitrio should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasitrio (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to other dihydropyridine derivatives, or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2).
- Hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia and refractory hypokalaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

General
In the event of severe and persistent diarrhoea, Rasitrio therapy should be stopped (see section 4.8).

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended. Close monitoring of blood pressure, renal function and electrolytes should be exercised if co-administration is considered absolutely necessary.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

Geriatric patients aged 65 years and over
Particular caution should be exercised when administering Rasitrio in patients aged 65 years or older. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Patients aged 65 years old or over, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2).

Geriatric patients aged 75 years and over
Very limited efficacy and safety data are available on the use of Rasitrio in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.2, 4.8, 5.1 and 5.2).

Heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

No data on cardiovascular mortality and morbidity are available for Rasitrio in patients with heart failure (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasitrio in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or
- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasitrio, or the treatment should start under close medical supervision.

Electrolyte imbalance

Treatment with Rasitrio should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy Rasitrio should be discontinued until stable correction of the potassium balance.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3, 4.5 and 4.8).

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Rasitrio therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

There is no evidence that Rasitrio would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Renal impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasitrio is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. No data is available in hypertensive patients with severe renal impairment (serum creatinine ≥150 µmol/l or 1.70 mg/dl in women and ≥177 µmol/l or 2.00 mg/dl in men and/or estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Rasitrio is contraindicated in hypertensive patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) or anuria (see sections 4.2. and 4.3). No dose adjustment is necessary in patients with mild to moderate renal impairment.

As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients.

Hepatic impairment
Rasitrio is contraindicated in hypertensive patients with severe hepatic impairment (see sections 4.3 and 5.2). Caution should be exercised when administering Rasitrio to patients with mild to moderate hepatic impairment or progressive liver disease (see sections 4.2 and 5.2).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dose adjustments of insulin or oral hypoglycaemic medicinal products may be required during Rasitrio therapy. Concomitant use of Rasitrio with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Rasitrio is contraindicated in symptomatic hyperuricaemia (see section 4.3). Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis
No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema
Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). As with other medicinal products acting on the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal products that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, Rasitrio should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasitrio, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of treatment initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasitrio interactions
A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) and C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocoricotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Rasitrio is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Rasitrio with an NSAID requires caution, especially in elderly patients.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *Dual RAAS blockade*

The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *P-glycoprotein (P-gp) potent inhibitors*

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended (see section 4.2)
- *Grapefruit juice*

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio.

Caution required with concomitant use

- *P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

- *Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

- *Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

- *Food interactions*

Meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially (see section 4.2).

No interactions

- Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

- Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. Co-administration of aliskiren had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

- Digoxin and verapamil bioavailability may be slightly decreased by aliskiren.

- *CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

- *P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

- *Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

- *CYP3A4 inducers*

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

- *Grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

- *Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

- The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other antihypertensive medicinal products.

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

No interactions

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Information on hydrochlorothiazide interactions

When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Not recommended

- *Lithium*

Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Caution required with concomitant use

- *Alcohol, barbiturates or narcotics*

Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

- *Amantadine*

Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

- *Antidiabetic agents (e.g. insulin and oral antidiabetic agents)*

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

- *Anticholinergic agents and other medicinal products affecting gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.

- *Medicinal products used in the treatment of gout*

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

- *Medicinal products that could induce torsades de pointes*

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

- *Medicinal products affecting serum sodium level*

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

- *Beta blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

- *Ion exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

- *Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy, or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

- *Non-depolarising skeletal muscle relaxants*

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

- *Cytotoxic agents*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

- *Digoxine or digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

- *Methyldopa*

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

- *Iodine contrasting agents*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

- *Pressor amines (e.g. noradrenaline, adrenaline)*

Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant.

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the renin-angiotensin-aldosterone system have been associated with serious foetal malformations and neonatal death. As for any medicinal product that acts directly on the renin-angiotensin-aldosterone system, aliskiren should not be used during the first trimester of pregnancy and is contraindicated during the second and third trimesters (see section 4.3).

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3).

If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible.

Breast-feeding

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Rasitrio during breast-feeding is not recommended. If Rasitrio is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility with the use of Rasitrio.

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3). The fertility of rats was unaffected at doses of up to aliskiren 250 mg/kg/day and hydrochlorothiazide 4 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, drowsiness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

Aliskiren/amlodipine/hydrochlorothiazide combination
The safety profile of Rasitrio presented below is based on clinical studies performed with Rasitrio and the known safety profile of the individual components aliskiren, amlodipine and hydrochlorothiazide. Safety information for Rasitrio in patients aged 75 years and older is limited.

The most frequent adverse reactions observed with Rasitrio are hypotension and dizziness. The adverse reactions previously reported with one of the individual components of Rasitrio (aliskiren, amlodipine and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Rasitrio.

Tabulated list of adverse reactions:
The adverse reactions for aliskiren, amlodipine and hydrochlorothiazide are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Information on Rasitrio

Nervous system disorders	
Common	Dizziness
Vascular disorders	
Common	Hypotension
General disorders and administration site conditions	
Common	Peripheral oedema

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The incidence of peripheral oedema for Rasitrio in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

The incidence of any adverse reactions potentially related to hypotension in a short-term active controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Rasitrio even if not observed in clinical trials.

Aliskiren
Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:
The known aliskiren adverse reactions are presented in the table below using the same convention as described previously for the fixed combination.

Immune system disorders		
	Rare	Anaphylactic reactions, hypersensitivity reactions
Cardiac disorders		
	Common	Dizziness
	Uncommon	Palpitations, oedema peripheral
Vascular disorders		
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Cough
Gastrointestinal disorders		
	Common	Diarrhoea
Hepatobiliary disorders		
	Not known	Liver disorder*, jaundice, hepatitis, liver failure**
Skin and subcutaneous tissue disorders		
	Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN), oral mucosal reactions, rash, pruritus, urticaria
	Rare	Angioedema, erythema
Musculoskeletal and connective tissue disorders		
	Common	Arthralgia
Renal and urinary disorders		
	Uncommon	Acute renal failure, renal impairment
Investigations		
	Common	Hyperkalaemia
	Uncommon	Liver enzyme increased
	Rare	Haemoglobin decreased, haematocrit decreased, blood creatinine increased

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.
**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse events:
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicinal products known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing, or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

Investigations: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other medicinal products acting on the RAAS, such as ACEIs and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Paediatric population: Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.

Amlodipine

Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes (including anxiety), depression
Rare	Confusion
Nervous system disorders	
Common	Somnolence, headache (especially at the beginning of treatment)
Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Eye disorders	
Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	
Common	Flushing
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, purpura, skin decolouration, hyperhidrosis, pruritus, rash, exanthema
Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Ankle swelling
Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Chest pain, asthenia, pain, malaise
Investigations	
Uncommon	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasitrio. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare	Thrombocytopenia sometimes with purpura
	Very rare	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known	Aplastic anaemia
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Hypokalaemia
	Common	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare	Depression, sleep disturbances
Nervous system disorders		
	Rare	Dizziness, headache, paraesthesia
Eye disorders		
	Rare	Visual impairment
	Not known	Acute angle-closure glaucoma
Cardiac disorders		
	Rare	Cardiac arrhythmias
Vascular disorders		
	Common	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common	Decreased appetite, mild nausea and vomiting
	Rare	Abdominal discomfort, constipation, diarrhoea
	Very rare	Pancreatitis
Hepatobiliary disorders		
	Rare	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common	Urticaria and other forms of rash
	Rare	Photosensitivity reactions
	Very rare	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known	Muscle spasm
Renal and urinary disorders		
	Not known	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common	Impotence
General disorders and administration site conditions		
	Not known	Asthenia, pyrexia
Investigations		
	Very common	Increases in cholesterol and triglycerides
	Rare	Glycosuria

4.9 Overdose

Symptoms
The most likely manifestation of overdose for Rasitrio would be hypotension, related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

With aliskiren, the most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

With amlodipine, available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome, have been reported with amlodipine.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products.

Treatment
If symptomatic hypotension should occur with Rasitrio, supportive treatment should be initiated.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin-inhibitors; ATC code C09XA54

Rasitrio combines three antihypertensive active substances with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine to the calcium channel blocker class and hydrochlorothiazide to the thiazide diuretics class. When combined, the consolidated effects of inhibition of the renin-angiotensin-aldosterone system, calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combinations.

Aliskiren/amlodipine/hydrochlorothiazide combination
In hypertensive patients, once-daily administration of Rasitrio provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for Rasitrio over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

Rasitrio was studied in a double-blind, randomised, active-controlled study in 1,181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP >180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes. During the first 4 weeks of double-blind treatment, patients received triple combination aliskiren/amlodipine/hydrochlorothiazide (HCTZ) 150/5/12.5 mg (N=308), or dual combinations of aliskiren/HCTZ 150/12.5 mg (N=295), aliskiren/amlodipine 150/5 mg (N=282) and amlodipine/HCTZ 5/12.5 mg (N=295). Patients were force-titrated to higher doses after 4 weeks for an additional 4 weeks of double-blind treatment to aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg and amlodipine/HCTZ 10/25 mg.

In this study, Rasitrio at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥180 mmHg), the reduction in blood pressure from baseline for Rasitrio and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). In a subset of 588 patients in which patients >65 years were scarcely represented and those aged >75 years were very scarcely represented, the combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) produced a systolic/diastolic mean blood pressure reduction of 39.7/21.1 mmHg from baseline, compared to 31.3/18.74 mmHg for aliskiren/amlodipine (300/10 mg), 25.5/12.5 mmHg for aliskiren/hydrochlorothiazide (300/25 mg) and 29.2/16.4 mmHg for amlodipine/hydrochlorothiazide (10/25 mg) (the subset constitutes patients without aberrant readings, defined as a difference between systolic blood pressure (SBP) readings ≥10 mmHg at baseline or endpoint). The effect of Rasitrio was observed as early as one week after initiation of therapy. The blood-pressure-lowering effect in patients with moderate to severe hypertension was independent of age, gender, race, body mass index and overweight-associated disorders (metabolic syndrome and diabetes).

Rasitrio was associated with a significant reduction in plasma renin activity (PRA) (-34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA (+170%). The clinical implications of the differences in effect on PRA are not known at the present time.

In a 28 to 54 week open label safety study, efficacy was measured as secondary endpoint and Rasitrio at a dose of 300/10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of Rasitrio was maintained over one year of treatment, with no evidence of loss of effect.

In a randomised, double blind, active controlled, 36-week study in elderly patients whose blood pressure was not controlled with aliskiren/HCTZ 300/25 mg (SBP ≥140 mmHg), clinically meaningful further BP reduction was seen at week 36 endpoint for patients who received Rasitrio at a dose of 300/10/25 mg (from reductions in msSBP/msDBP of 15.0/8.6 mmHg at week 22 to reductions of 30.8/14.1 mmHg at week 36 endpoint).

Rasitrio has been administered to more than 1,155 patients in completed clinical trials, including 182 patients for one year or more. Treatment with Rasitrio was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar to the corresponding dual combinations, except for symptomatic hypotension. The incidence of any adverse reactions potentially related to hypotension in a short-term controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

The incidence of adverse events did not show any association with gender, age (with the exception of symptomatic hypotension), body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Very limited safety data are available for patients aged >75 years or patients with major cardiovascular co-morbidities. Discontinuation of therapy due to a clinical adverse event occurred in 3.6% of patients treated with Rasitrio versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other medicinal products that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive medicinal products. The clinical implications of the differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood-pressure-lowering effects comparable to other classes of antihypertensive medicinal products including selected ACEI and ARB. Compared to a diuretic (hydrochlorothiazide, HCTZ), aliskiren 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Aliskiren induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12-week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In an 8-week study in 754 hypertensive geriatric patients aged 65 years or older and geriatric patients aged 75 years or older (30%) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive medicinal products. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR <60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Study results indicated a hazard ratio for the primary endpoint of 1.11 in favour of placebo (95% Confidence Interval: 1.00, 1.23, 2-sided p=0.05). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (37.9% versus 30.2%). In particular there was an increased incidence of renal dysfunction (14.0% versus 12.1%), hyperkalaemia (38.9% versus 28.8%), hypotension-related events (19.7% versus 16.2%) and adjudicated stroke endpoints (3.4% versus 2.6%). The increased incidence of stroke was greater in patients with renal insufficiency.

Effects of aliskiren on mortality and cardiovascular morbidity are currently unknown.

No long-term efficacy data for aliskiren in patients with heart failure are currently available (see section 4.4).

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Amlodipine
The amlodipine component of Rasitrio inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Use in patients with heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasitrio in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Aliskiren/amlodipine/hydrochlorothiazide combination
Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Aliskiren
Absorption
Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and AUC $_{0\text{-}tau}$ by 67% in hypertensive patients. Steady-state plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution
Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation and elimination
The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients (aged 6-17 years) given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The available data did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

<u>Amlodipine</u>
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
The volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days.

Linearity
Amlodipine exhibits linear pharmacokinetics between the therapeutic dose range of 5 mg and 10 mg.

<u>Hydrochlorothiazide</u>
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Linearity
The increase in mean AUC is linear and dose proportional in the therapeutic range.

Special populations
Rasitrio is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

Renal impairment
Due to its hydrochlorothiazide component, Rasitrio is contraindicated in patients with anuria or severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.3). No adjustment of the initial dose is required in patients with mild to moderate renal impairment (see sections 4.4 and 4.2).

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dose of aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2). Concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment (see section 4.3).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to moderate hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised in patients with hepatic impairment.

Geriatric patients
No data are available on systemic exposure after administration of Rasitrio in geriatric patients. When administered alone, the AUC of aliskiren in geriatric subjects (>65 years) is 50% higher than in young subjects. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in geriatric patients. Therefore particular caution is recommended when administering Rasitrio to patients aged 65 years and over, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. There are no specific data regarding the effect of hydrochlorothiazide in elderly patients.

Paediatric population (age below 18 years)
The pharmacokinetics of Rasitrio have not been investigated. A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

5.3 Preclinical safety data

Aliskiren/hydrochlorothiazide and aliskiren/amlodipine
Non-clinical studies of the toxicology of Rasitrio alone have not been conducted as these studies have been conducted for the individual components.

The toxicity profiles of the combination of aliskiren/hydrochlorothiazide and aliskiren/amlodipine have been well characterised in preclinical studies. Both combinations were generally well tolerated by rats. The findings from 2- and 13-week oral toxicity studies were consistent with those for the individual components.

Aliskiren
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically.

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no effects related to the medicinal product at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Hydrochlorothiazide

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg,/day respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/polychlorotrifluoroethylene (PCTFE) – Alu calendar blisters:
2 years

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
2 years

PA/Alu/PVC – Alu calendar blisters:
18 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets

PVC/polychlorotrifluoroethylene (PCTFE) - Alu blisters:
Single pack containing 30, 90 tablets
Unit dose pack (perforated unit dose blister) containing 56x1 tablet
Multipacks of unit dose (perforated unit dose blister) containing 98x1 tablet (2 packs of 49x1)

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multipacks containing 98 tablets (2 packs of 49)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/025-036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate), 10 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light red, ovaloid convex film-coated tablet with bevelled edges, with “UIU” debossed on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology
The recommended dose of Rasitrio is one tablet per day.

Patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets given concurrently at the same time of the day may be switched to a fixed combination tablet of Rasitrio containing the same component doses.

The fixed dose combination should only be used after a stable effect on the monocomponents, given concurrently, has been established after dose titration. Dose should be individualised and adjusted according to the patient’s clinical response.

Special populations
Elderly patients aged 65 years and over
There is evidence of an increased risk of adverse events related to hypotension in patients aged 65 years or older treated with Rasitrio. Therefore, particular caution should be exercised when administering Rasitrio in patients aged 65 years or over.

The recommended starting dose of aliskiren in this group of patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Elderly patients aged 75 years and over
Very limited data are available on the use of Rasitrio in patients aged 75 years or older (see section 5.2). The use of Rasitrio in patients aged 75 years or older should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.4, 4.8, 5.1 and 5.2).

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate (GFR) 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively) (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Rasitrio is contraindicated for use in patients with anuria and in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2). The concomitant use of Rasitrio with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Rasitrio in patients with mild to moderate hepatic impairment or patients with progressive liver disease. No dosage recommendations have been established for amlodipine in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasitrio should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasitrio (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to other dihydropyridine derivatives, or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2).
- Hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia and refractory hypokalaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

General
In the event of severe and persistent diarrhoea, Rasitrio therapy should be stopped (see section 4.8).

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended. Close monitoring of blood pressure, renal function and electrolytes should be exercised if co-administration is considered absolutely necessary.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

Geriatric patients aged 65 years and over
Particular caution should be exercised when administering Rasitrio in patients aged 65 years or older. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Patients aged 65 years old or over, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2).

Geriatric patients aged 75 years and over
Very limited efficacy and safety data are available on the use of Rasitrio in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.2, 4.8, 5.1 and 5.2).

Heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

No data on cardiovascular mortality and morbidity are available for Rasitrio in patients with heart failure (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasitrio in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or
- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasitrio, or the treatment should start under close medical supervision.

Electrolyte imbalance

Treatment with Rasitrio should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy Rasitrio should be discontinued until stable correction of the potassium balance.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3, 4.5 and 4.8).

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Rasitrio therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

There is no evidence that Rasitrio would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Renal impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasitrio is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. No data is available in hypertensive patients with severe renal impairment (serum creatinine ≥150 μmol/l or 1.70 mg/dl in women and ≥177 μmol/l or 2.00 mg/dl in men and/or estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Rasitrio is contraindicated in hypertensive patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) or anuria (see sections 4.2. and 4.3). No dose adjustment is necessary in patients with mild to moderate renal impairment.

As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients.

Hepatic impairment
Rasitrio is contraindicated in hypertensive patients with severe hepatic impairment (see sections 4.3 and 5.2). Caution should be exercised when administering Rasitrio to patients with mild to moderate hepatic impairment or progressive liver disease (see sections 4.2 and 5.2).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dose adjustments of insulin or oral hypoglycaemic medicinal products may be required during Rasitrio therapy. Concomitant use of Rasitrio with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Rasitrio is contraindicated in symptomatic hyperuricaemia (see section 4.3). Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis
No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema
Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). As with other medicinal products acting on the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal products that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, Rasitrio should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasitrio, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of treatment initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasitrio interactions
A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) and C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocoricotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Rasitrio is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Rasitrio with an NSAID requires caution, especially in elderly patients.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *Dual RAAS blockade*

The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *P-glycoprotein (P-gp) potent inhibitors*

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended (see section 4.2)
- *Grapefruit juice*

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio.

Caution required with concomitant use

- *P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

- *Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

- *Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

- *Food interactions*

Meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially (see section 4.2).

No interactions

- Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

- Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. Co-administration of aliskiren had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

- Digoxin and verapamil bioavailability may be slightly decreased by aliskiren.

- *CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

- *P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

- *Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

- *CYP3A4 inducers*

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

- *Grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

- *Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

- The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other antihypertensive medicinal products.

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

No interactions

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Information on hydrochlorothiazide interactions

When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Not recommended

- *Lithium*

Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Caution required with concomitant use

- *Alcohol, barbiturates or narcotics*

Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

- *Amantadine*

Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

- *Antidiabetic agents (e.g. insulin and oral antidiabetic agents)*

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

- *Anticholinergic agents and other medicinal products affecting gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.

- *Medicinal products used in the treatment of gout*

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

- *Medicinal products that could induce torsades de pointes*

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

- *Medicinal products affecting serum sodium level*

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

- *Beta blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

- *Ion exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

- *Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy, or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

- *Non-depolarising skeletal muscle relaxants*

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

- *Cytotoxic agents*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

- *Digoxine or digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

- *Methyldopa*

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

- *Iodine contrasting agents*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

- *Pressor amines (e.g. noradrenaline, adrenaline)*

Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant.

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the renin-angiotensin-aldosterone system have been associated with serious foetal malformations and neonatal death. As for any medicinal product that acts directly on the renin-angiotensin-aldosterone system, aliskiren should not be used during the first trimester of pregnancy and is contraindicated during the second and third trimesters (see section 4.3).

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3).

If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible.

Breast-feeding

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Rasitrio during breast-feeding is not recommended. If Rasitrio is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility with the use of Rasitrio.

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3). The fertility of rats was unaffected at doses of up to aliskiren 250 mg/kg/day and hydrochlorothiazide 4 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, drowsiness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

Aliskiren/amlodipine/hydrochlorothiazide combination
The safety profile of Rasitrio presented below is based on clinical studies performed with Rasitrio and the known safety profile of the individual components aliskiren, amlodipine and hydrochlorothiazide. Safety information for Rasitrio in patients aged 75 years and older is limited.

The most frequent adverse reactions observed with Rasitrio are hypotension and dizziness. The adverse reactions previously reported with one of the individual components of Rasitrio (aliskiren, amlodipine and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Rasitrio.

Tabulated list of adverse reactions:
The adverse reactions for aliskiren, amlodipine and hydrochlorothiazide are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Information on Rasitrio

Nervous system disorders		
	Common	Dizziness
Vascular disorders		
	Common	Hypotension
General disorders and administration site conditions		
	Common	Peripheral oedema

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The incidence of peripheral oedema for Rasitrio in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

The incidence of any adverse reactions potentially related to hypotension in a short-term active controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Rasitrio even if not observed in clinical trials.

Aliskiren
Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:
The known aliskiren adverse reactions are presented in the table below using the same convention as described previously for the fixed combination.

Immune system disorders		
	Rare	Anaphylactic reactions, hypersensitivity reactions
Cardiac disorders		
	Common	Dizziness
	Uncommon	Palpitations, oedema peripheral
Vascular disorders		
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Cough
Gastrointestinal disorders		
	Common	Diarrhoea
Hepatobiliary disorders		
	Not known	Liver disorder*, jaundice, hepatitis, liver failure**
Skin and subcutaneous tissue disorders		
	Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN), oral mucosal reactions, rash, pruritus, urticaria
	Rare	Angioedema, erythema
Musculoskeletal and connective tissue disorders		
	Common	Arthralgia
Renal and urinary disorders		
	Uncommon	Acute renal failure, renal impairment
Investigations		
	Common	Hyperkalaemia
	Uncommon	Liver enzyme increased
	Rare	Haemoglobin decreased, haematocrit decreased, blood creatinine increased

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.
**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse events:
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicinal products known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing, or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

Investigations: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other medicinal products acting on the RAAS, such as ACEIs and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Paediatric population: Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.

Amlodipine

Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes (including anxiety), depression
Rare	Confusion
Nervous system disorders	
Common	Somnolence, headache (especially at the beginning of treatment)
Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Eye disorders	
Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	
Common	Flushing
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, purpura, skin decolouration, hyperhidrosis, pruritus, rash, exanthema
Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Ankle swelling
Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Chest pain, asthenia, pain, malaise
Investigations	
Uncommon	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasitrio. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare	Thrombocytopenia sometimes with purpura
	Very rare	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known	Aplastic anaemia
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Hypokalaemia
	Common	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare	Depression, sleep disturbances
Nervous system disorders		
	Rare	Dizziness, headache, paraesthesia
Eye disorders		
	Rare	Visual impairment
	Not known	Acute angle-closure glaucoma
Cardiac disorders		
	Rare	Cardiac arrhythmias
Vascular disorders		
	Common	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common	Decreased appetite, mild nausea and vomiting
	Rare	Abdominal discomfort, constipation, diarrhoea
	Very rare	Pancreatitis
Hepatobiliary disorders		
	Rare	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common	Urticaria and other forms of rash
	Rare	Photosensitivity reactions
	Very rare	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known	Muscle spasm
Renal and urinary disorders		
	Not known	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common	Impotence
General disorders and administration site conditions		
	Not known	Asthenia, pyrexia
Investigations		
	Very common	Increases in cholesterol and triglycerides
	Rare	Glycosuria

4.9 Overdose

Symptoms
The most likely manifestation of overdose for Rasitrio would be hypotension, related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

With aliskiren, the most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

With amlodipine, available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome, have been reported with amlodipine.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products.

Treatment
If symptomatic hypotension should occur with Rasitrio, supportive treatment should be initiated.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin-inhibitors; ATC code C09XA54

Rasitrio combines three antihypertensive active substances with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine to the calcium channel blocker class and hydrochlorothiazide to the thiazide diuretics class. When combined, the consolidated effects of inhibition of the renin-angiotensin-aldosterone system, calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combinations.

Aliskiren/amlodipine/hydrochlorothiazide combination
In hypertensive patients, once-daily administration of Rasitrio provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for Rasitrio over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

Rasitrio was studied in a double-blind, randomised, active-controlled study in 1,181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP >180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes. During the first 4 weeks of double-blind treatment, patients received triple combination aliskiren/amlodipine/hydrochlorothiazide (HCTZ) 150/5/12.5 mg (N=308), or dual combinations of aliskiren/HCTZ 150/12.5 mg (N=295), aliskiren/amlodipine 150/5 mg (N=282) and amlodipine/HCTZ 5/12.5 mg (N=295). Patients were force-titrated to higher doses after 4 weeks for an additional 4 weeks of double-blind treatment to aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg and amlodipine/HCTZ 10/25 mg.

In this study, Rasitrio at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥180 mmHg), the reduction in blood pressure from baseline for Rasitrio and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). In a subset of 588 patients in which patients >65 years were scarcely represented and those aged >75 years were very scarcely represented, the combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) produced a systolic/diastolic mean blood pressure reduction of 39.7/21.1 mmHg from baseline, compared to 31.3/18.74 mmHg for aliskiren/amlodipine (300/10 mg), 25.5/12.5 mmHg for aliskiren/hydrochlorothiazide (300/25 mg) and 29.2/16.4 mmHg for amlodipine/hydrochlorothiazide (10/25 mg) (the subset constitutes patients without aberrant readings, defined as a difference between systolic blood pressure (SBP) readings ≥10 mmHg at baseline or endpoint). The effect of Rasitrio was observed as early as one week after initiation of therapy. The blood-pressure-lowering effect in patients with moderate to severe hypertension was independent of age, gender, race, body mass index and overweight-associated disorders (metabolic syndrome and diabetes).

Rasitrio was associated with a significant reduction in plasma renin activity (PRA) (-34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA (+170%). The clinical implications of the differences in effect on PRA are not known at the present time.

In a 28 to 54 week open label safety study, efficacy was measured as secondary endpoint and Rasitrio at a dose of 300/10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of Rasitrio was maintained over one year of treatment, with no evidence of loss of effect.

In a randomised, double blind, active controlled, 36-week study in elderly patients whose blood pressure was not controlled with aliskiren/HCTZ 300/25 mg (SBP ≥140 mmHg), clinically meaningful further BP reduction was seen at week 36 endpoint for patients who received Rasitrio at a dose of 300/10/25 mg (from reductions in msSBP/msDBP of 15.0/8.6 mmHg at week 22 to reductions of 30.8/14.1 mmHg at week 36 endpoint).

Rasitrio has been administered to more than 1,155 patients in completed clinical trials, including 182 patients for one year or more. Treatment with Rasitrio was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar to the corresponding dual combinations, except for symptomatic hypotension. The incidence of any adverse reactions potentially related to hypotension in a short-term controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

The incidence of adverse events did not show any association with gender, age (with the exception of symptomatic hypotension), body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Very limited safety data are available for patients aged >75 years or patients with major cardiovascular co-morbidities. Discontinuation of therapy due to a clinical adverse event occurred in 3.6% of patients treated with Rasitrio versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other medicinal products that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive medicinal products. The clinical implications of the differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood-pressure-lowering effects comparable to other classes of antihypertensive medicinal products including selected ACEI and ARB. Compared to a diuretic (hydrochlorothiazide, HCTZ), aliskiren 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Aliskiren induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12-week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In an 8-week study in 754 hypertensive geriatric patients aged 65 years or older and geriatric patients aged 75 years or older (30%) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive medicinal products. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR <60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Study results indicated a hazard ratio for the primary endpoint of 1.11 in favour of placebo (95% Confidence Interval: 1.00, 1.23, 2-sided p=0.05). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (37.9% versus 30.2%). In particular there was an increased incidence of renal dysfunction (14.0% versus 12.1%), hyperkalaemia (38.9% versus 28.8%), hypotension-related events (19.7% versus 16.2%) and adjudicated stroke endpoints (3.4% versus 2.6%). The increased incidence of stroke was greater in patients with renal insufficiency.

Effects of aliskiren on mortality and cardiovascular morbidity are currently unknown.

No long-term efficacy data for aliskiren in patients with heart failure are currently available (see section 4.4).

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Amlodipine
The amlodipine component of Rasitrio inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Use in patients with heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasitrio in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Aliskiren/amlodipine/hydrochlorothiazide combination
Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Aliskiren
Absorption
Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and AUC $_{0-tau}$ by 67% in hypertensive patients. Steady-state plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution
Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation and elimination
The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients (aged 6-17 years) given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The available data did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

Amlodipine
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
The volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days.

Linearity
Amlodipine exhibits linear pharmacokinetics between the therapeutic dose range of 5 mg and 10 mg.

Hydrochlorothiazide
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Linearity
The increase in mean AUC is linear and dose proportional in the therapeutic range.

Special populations
Rasitrio is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

Renal impairment
Due to its hydrochlorothiazide component, Rasitrio is contraindicated in patients with anuria or severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.3). No adjustment of the initial dose is required in patients with mild to moderate renal impairment (see sections 4.4 and 4.2).

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dose of aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2). Concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment (see section 4.3).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to moderate hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised in patients with hepatic impairment.

Geriatric patients
No data are available on systemic exposure after administration of Rasitrio in geriatric patients. When administered alone, the AUC of aliskiren in geriatric subjects (>65 years) is 50% higher than in young subjects. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in geriatric patients. Therefore particular caution is recommended when administering Rasitrio to patients aged 65 years and over, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. There are no specific data regarding the effect of hydrochlorothiazide in elderly patients.

Paediatric population (age below 18 years)
The pharmacokinetics of Rasitrio have not been investigated. A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

5.3 Preclinical safety data

Aliskiren/hydrochlorothiazide and aliskiren/amlodipine
Non-clinical studies of the toxicology of Rasitrio alone have not been conducted as these studies have been conducted for the individual components.

The toxicity profiles of the combination of aliskiren/hydrochlorothiazide and aliskiren/amlodipine have been well characterised in preclinical studies. Both combinations were generally well tolerated by rats. The findings from 2- and 13-week oral toxicity studies were consistent with those for the individual components.

Aliskiren
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically.

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no effects related to the medicinal product at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Hydrochlorothiazide

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg,/day respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/polychlorotrifluoroethylene (PCTFE) – Alu calendar blisters:
2 years

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
2 years

PA/Alu/PVC – Alu calendar blisters:
18 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets

PVC/polychlorotrifluoroethylene (PCTFE) - Alu blisters:
Single pack containing 30, 90 tablets
Unit dose pack (perforated unit dose blister) containing 56x1 tablet
Multipacks of unit dose (perforated unit dose blister) containing 98x1 tablet (2 packs of 49x1)

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multipacks containing 98 tablets (2 packs of 49)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/037-048

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate), 10 mg amlodipine (as besylate) and 25 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Brown, ovaloid convex film-coated tablet with bevelled edges, with “VIV” debossed on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasitrio is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently at the same dose level as in the combination.

4.2 Posology and method of administration

Posology
The recommended dose of Rasitrio is one tablet per day.

Patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets given concurrently at the same time of the day may be switched to a fixed combination tablet of Rasitrio containing the same component doses.

The fixed dose combination should only be used after a stable effect on the monocomponents, given concurrently, has been established after dose titration. Dose should be individualised and adjusted according to the patient’s clinical response.

Special populations
Elderly patients aged 65 years and over
There is evidence of an increased risk of adverse events related to hypotension in patients aged 65 years or older treated with Rasitrio. Therefore, particular caution should be exercised when administering Rasitrio in patients aged 65 years or over.

The recommended starting dose of aliskiren in this group of patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

Elderly patients aged 75 years and over
Very limited data are available on the use of Rasitrio in patients aged 75 years or older (see section 5.2). The use of Rasitrio in patients aged 75 years or older should be restricted to patients for whom blood pressure control has been established for the free combination of aliskiren, amlodipine and hydrochlorothiazide given concurrently without accompanying safety concerns, in particular hypotension. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.4, 4.8, 5.1 and 5.2).

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate (GFR) 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively) (see sections 4.4 and 5.2). Due to the hydrochlorothiazide component, Rasitrio is contraindicated for use in patients with anuria and in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2). The concomitant use of Rasitrio with angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Rasitrio in patients with mild to moderate hepatic impairment or patients with progressive liver disease. No dosage recommendations have been established for amlodipine in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of Rasitrio in children and adolescents below age 18 have not been established. No data are available.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasitrio should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasitrio (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to other dihydropyridine derivatives, or to other sulphonamide-derived substances.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- Anuria.
- Severe renal impairment (GFR <30 ml/min/1.73 m^2).
- Hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia and refractory hypokalaemia.
- Severe hepatic impairment.
- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).
- The concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5 and 5.1).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

General
In the event of severe and persistent diarrhoea, Rasitrio therapy should be stopped (see section 4.8).

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients, but are more likely in patients with allergy and asthma.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended. Close monitoring of blood pressure, renal function and electrolytes should be exercised if co-administration is considered absolutely necessary.

The use of aliskiren in combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

Geriatric patients aged 65 years and over
Particular caution should be exercised when administering Rasitrio in patients aged 65 years or older. Symptomatic hypotension occurred with higher frequency in patients with non-complicated hypertension treated with Rasitrio than in patients treated with dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide. Patients aged 65 years old or over, are more susceptible to hypotension-related adverse reactions following treatment with Rasitrio (see sections 4.2, 4.8, 5.1 and 5.2).

Geriatric patients aged 75 years and over
Very limited efficacy and safety data are available on the use of Rasitrio in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended (see sections 4.2, 4.8, 5.1 and 5.2).

Heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

No data on cardiovascular mortality and morbidity are available for Rasitrio in patients with heart failure (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasitrio in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or
- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasitrio, or the treatment should start under close medical supervision.

Electrolyte imbalance

Treatment with Rasitrio should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy Rasitrio should be discontinued until stable correction of the potassium balance.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greater in patients with cirrhosis of the liver, patients experiencing brisk diuresis, patients with inadequate oral electrolyte intake and patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) (see sections 4.5 and 4.8).

Conversely, increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3, 4.5 and 4.8).

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Rasitrio therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

There is no evidence that Rasitrio would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Renal impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasitrio is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. No data is available in hypertensive patients with severe renal impairment (serum creatinine ≥150 μmol/l or 1.70 mg/dl in women and ≥177 μmol/l or 2.00 mg/dl in men and/or estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. Rasitrio is contraindicated in hypertensive patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) or anuria (see sections 4.2. and 4.3). No dose adjustment is necessary in patients with mild to moderate renal impairment.

As for other medicinal products acting on the RAAS, caution should be exercised when Rasitrio is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe or prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. The concomitant use of aliskiren and ACEIs or ARBs is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2). Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

There is no experience regarding the administration of Rasitrio in patients who have recently undergone kidney transplantation, therefore caution should be exercised in these patients.

Hepatic impairment
Rasitrio is contraindicated in hypertensive patients with severe hepatic impairment (see sections 4.3 and 5.2). Caution should be exercised when administering Rasitrio to patients with mild to moderate hepatic impairment or progressive liver disease (see sections 4.2 and 5.2).

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides, and uric acid. In diabetic patients dose adjustments of insulin or oral hypoglycaemic medicinal products may be required during Rasitrio therapy. Concomitant use of Rasitrio with ARBs or ACEIs is contraindicated in patients with diabetes mellitus (see section 4.3).

Due to the hydrochlorothiazide component, Rasitrio is contraindicated in symptomatic hyperuricaemia (see section 4.3). Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Rasitrio is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasitrio should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Renal artery stenosis
No controlled clinical data are available on the use of Rasitrio in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other medicinal products acting on the renin-angiotensin-aldosterone system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema
Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). As with other medicinal products acting on the renin-angiotensin-aldosterone system (RAAS), angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal products that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, Rasitrio should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasitrio, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of treatment initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasitrio interactions
A population pharmacokinetic analysis in patients with hypertension did not indicate any clinically relevant changes in the steady-state exposure (AUC) and C_{max} of aliskiren, amlodipine and hydrochlorothiazide compared to the corresponding dual therapies.

Medicinal products affecting serum potassium levels: The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of aliskiren. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, corticosteroids, laxatives, adrenocoricotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives). Conversely, concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium is recommended when Rasitrio is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics).

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid and non-selective NSAIDs: As with other agents acting on the renin-angiotensin system, NSAIDs may reduce the antihypertensive effect of aliskiren. NSAIDs may also weaken the diuretic and antihypertensive activity of hydrochlorothiazide.

In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren and hydrochlorothiazide given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the use of Rasitrio with an NSAID requires caution, especially in elderly patients.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *Dual RAAS blockade*

The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *P-glycoprotein (P-gp) potent inhibitors*

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and C_{max} of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended (see section 4.2)
- *Grapefruit juice*

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasitrio.

Caution required with concomitant use

- *P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies. Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John's wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

- *Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

- *Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

- *Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

- *Food interactions*

Meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially (see section 4.2).

No interactions

- Compounds that have been investigated in aliskiren clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

- Co-administration of aliskiren with either metformin (↓28%), amlodipine (↑29%) or cimetidine (↑19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. When administered with atorvastatin, steady-state aliskiren AUC and C_{max} increased by 50%. Co-administration of aliskiren had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medicinal products is necessary.

- Digoxin and verapamil bioavailability may be slightly decreased by aliskiren.

- *CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

- *P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of aliskiren bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of aliskiren.

- *Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren when administered concomitantly (see interaction with Grapefruit juice).

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

- *CYP3A4 inducers*

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

- *Grapefruit juice*

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

- *Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

<u>*Effects of amlodipine on other medicinal products*</u>

- The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other antihypertensive medicinal products.

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

No interactions

- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

<u>Information on hydrochlorothiazide interactions</u>

When administered concurrently, the following medicinal products may interact with thiazide diuretics:

Not recommended

- *Lithium*

Renal clearance of lithium is reduced by thiazides, therefore the risk of lithium toxicity may be increased with hydrochlorothiazide. Co-administration of lithium and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Caution required with concomitant use

- *Alcohol, barbiturates or narcotics*

Concomitant administration of thiazide diuretics with subtances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.

- *Amantadine*

Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.

- *Antidiabetic agents (e.g. insulin and oral antidiabetic agents)*

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

- *Anticholinergic agents and other medicinal products affecting gastric motility*

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.

- *Medicinal products used in the treatment of gout*

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

- *Medicinal products that could induce torsades de pointes*

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

- *Medicinal products affecting serum sodium level*

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

- *Beta blockers and diazoxide*

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

- *Ion exchange resins*

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.

- *Vitamin D and calcium salts*

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy, or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

- *Non-depolarising skeletal muscle relaxants*

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

- *Cytotoxic agents*

Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

- *Digoxine or digitalis glycosides*

Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

- *Methyldopa*

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

- *Iodine contrasting agents*

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

- *Pressor amines (e.g. noradrenaline, adrenaline)*

Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Healthcare professionals prescribing Rasitrio should counsel women of childbearing potential about the potential risk during pregnancy. A switch to a suitable alternative antihypertensive treatment should be carried out in advance of a planned pregnancy since Rasitrio should not be used in women planning to become pregnant.

Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the renin-angiotensin-aldosterone system have been associated with serious foetal malformations and neonatal death. As for any medicinal product that acts directly on the renin-angiotensin-aldosterone system, aliskiren should not be used during the first trimester of pregnancy and is contraindicated during the second and third trimesters (see section 4.3).

The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Rasitrio should not be used during the first trimester of pregnancy. Rasitrio is contraindicated during the second and third trimesters (see section 4.3).

If pregnancy is detected during therapy, Rasitrio should be discontinued accordingly as soon as possible.

Breast-feeding

It is not known whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production.

The use of Rasitrio during breast-feeding is not recommended. If Rasitrio is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility with the use of Rasitrio.

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3). The fertility of rats was unaffected at doses of up to aliskiren 250 mg/kg/day and hydrochlorothiazide 4 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasitrio.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, drowsiness, headache, fatigue or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

Aliskiren/amlodipine/hydrochlorothiazide combination
The safety profile of Rasitrio presented below is based on clinical studies performed with Rasitrio and the known safety profile of the individual components aliskiren, amlodipine and hydrochlorothiazide. Safety information for Rasitrio in patients aged 75 years and older is limited.

The most frequent adverse reactions observed with Rasitrio are hypotension and dizziness. The adverse reactions previously reported with one of the individual components of Rasitrio (aliskiren, amlodipine and hydrochlorothiazide) and listed in the respective paragraphs on the individual components may occur with Rasitrio.

Tabulated list of adverse reactions:
The adverse reactions for aliskiren, amlodipine and hydrochlorothiazide are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Information on Rasitrio

Nervous system disorders	
Common	Dizziness
Vascular disorders	
Common	Hypotension
General disorders and administration site conditions	
Common	Peripheral oedema

Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The incidence of peripheral oedema for Rasitrio in a short-term double active-controlled study was 7.1% compared to 8.0% for aliskiren/amlodipine, 4.1% for amlodipine/hydrochlorothiazide and 2.0% for aliskiren/hydrochlorothiazide dual combinations.

The incidence of any adverse reactions potentially related to hypotension in a short-term active controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

Additional information on individual components
Other adverse reactions previously reported with one of the individual components may occur with Rasitrio even if not observed in clinical trials.

Aliskiren
Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:
The known aliskiren adverse reactions are presented in the table below using the same convention as described previously for the fixed combination.

Immune system disorders		
	Rare	Anaphylactic reactions, hypersensitivity reactions
Cardiac disorders		
	Common	Dizziness
	Uncommon	Palpitations, oedema peripheral
Vascular disorders		
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Cough
Gastrointestinal disorders		
	Common	Diarrhoea
Hepatobiliary disorders		
	Not known	Liver disorder*, jaundice, hepatitis, liver failure**
Skin and subcutaneous tissue disorders		
	Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN), oral mucosal reactions, rash, pruritus, urticaria
	Rare	Angioedema, erythema
Musculoskeletal and connective tissue disorders		
	Common	Arthralgia
Renal and urinary disorders		
	Uncommon	Acute renal failure, renal impairment
Investigations		
	Common	Hyperkalaemia
	Uncommon	Liver enzyme increased
	Rare	Haemoglobin decreased, haematocrit decreased, blood creatinine increased

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.
**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse events:
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical trials, angioedema and hypersensitivity reactions occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicinal products known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing, or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in patients at risk (see section 4.4).

Investigations: In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, aliskiren had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other medicinal products acting on the RAAS, such as ACEIs and ARBs.

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary. The combination of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4 and 5.1).

Paediatric population: Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.

Amlodipine

Blood and lymphatic system disorders	
Very rare	Leukopenia, thrombocytopenia
Immune system disorders	
Very rare	Allergic reactions
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes (including anxiety), depression
Rare	Confusion
Nervous system disorders	
Common	Somnolence, headache (especially at the beginning of treatment)
Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
Very rare	Hypertonia, peripheral neuropathy
Eye disorders	
Uncommon	Visual disturbance (including diplopia)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	
Common	Flushing
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice, hepatic enzymes increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, purpura, skin decolouration, hyperhidrosis, pruritus, rash, exanthema
Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Ankle swelling
Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Chest pain, asthenia, pain, malaise
Investigations	
Uncommon	Weight increase, weight decrease

Exceptional cases of extrapyramidal syndrome have been reported.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasitrio. The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Blood and lymphatic system disorders		
	Rare	Thrombocytopenia sometimes with purpura
	Very rare	Agranulocytosis, bone marrow depression, haemolytic anaemia, leucopenia
	Not known	Aplastic anaemia
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Hypokalaemia
	Common	Hyperuricaemia, hypomagnesaemia, hyponatraemia
	Rare	Hypercalcaemia, hyperglycaemia, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Psychiatric disorders		
	Rare	Depression, sleep disturbances
Nervous system disorders		
	Rare	Dizziness, headache, paraesthesia
Eye disorders		
	Rare	Visual impairment
	Not known	Acute angle-closure glaucoma
Cardiac disorders		
	Rare	Cardiac arrhythmias
Vascular disorders		
	Common	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		
	Very rare	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		
	Common	Decreased appetite, mild nausea and vomiting
	Rare	Abdominal discomfort, constipation, diarrhoea
	Very rare	Pancreatitis
Hepatobiliary disorders		
	Rare	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders		
	Common	Urticaria and other forms of rash
	Rare	Photosensitivity reactions
	Very rare	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, vasculitis necrotising and toxic epidermal necrolysis
	Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders		
	Not known	Muscle spasm
Renal and urinary disorders		
	Not known	Renal dysfunction, acute renal failure

Reproductive system and breast disorders		
	Common	Impotence
General disorders and administration site conditions		
	Not known	Asthenia, pyrexia
Investigations		
	Very common	Increases in cholesterol and triglycerides
	Rare	Glycosuria

4.9 Overdose

Symptoms
The most likely manifestation of overdose for Rasitrio would be hypotension, related to the antihypertensive effect of the combination of aliskiren, amlodipine and hydrochlorothiazide.

With aliskiren, the most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren.

With amlodipine, available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome, have been reported with amlodipine.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain antiarrhythmic medicinal products.

Treatment
If symptomatic hypotension should occur with Rasitrio, supportive treatment should be initiated.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Therefore dialysis is not adequate to treat aliskiren over-exposure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin-inhibitors; ATC code C09XA54

Rasitrio combines three antihypertensive active substances with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the direct renin inhibitor class, amlodipine to the calcium channel blocker class and hydrochlorothiazide to the thiazide diuretics class. When combined, the consolidated effects of inhibition of the renin-angiotensin-aldosterone system, calcium channel-mediated vasodilatation and sodium chloride excretion result in a reduction of blood pressure to a greater degree than the corresponding dual combinations.

Aliskiren/amlodipine/hydrochlorothiazide combination
In hypertensive patients, once-daily administration of Rasitrio provided clinically meaningful reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The greater blood pressure reduction for Rasitrio over each dual combination was seen at every hour including the early morning hours with the 24-hour ambulatory blood pressure monitoring.

Rasitrio was studied in a double-blind, randomised, active-controlled study in 1,181 patients of which 773 were classified as moderately hypertensive (msSBP 160-180 mmHg) and 408 as severely hypertensive (msSBP >180 mmHg) at baseline. A large number of patients were obese (49%) and over 14% of the total population had diabetes. During the first 4 weeks of double-blind treatment, patients received triple combination aliskiren/amlodipine/hydrochlorothiazide (HCTZ) 150/5/12.5 mg (N=308), or dual combinations of aliskiren/HCTZ 150/12.5 mg (N=295), aliskiren/amlodipine 150/5 mg (N=282) and amlodipine/HCTZ 5/12.5 mg (N=295). Patients were force-titrated to higher doses after 4 weeks for an additional 4 weeks of double-blind treatment to aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/HCTZ 300/25 mg, aliskiren/amlodipine 300/10 mg and amlodipine/HCTZ 10/25 mg.

In this study, Rasitrio at a dose of 300/10/25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) from baseline of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0 mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥180 mmHg), the reduction in blood pressure from baseline for Rasitrio and the dual combinations respectively was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). In a subset of 588 patients in which patients >65 years were scarcely represented and those aged >75 years were very scarcely represented, the combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) produced a systolic/diastolic mean blood pressure reduction of 39.7/21.1 mmHg from baseline, compared to 31.3/18.74 mmHg for aliskiren/amlodipine (300/10 mg), 25.5/12.5 mmHg for aliskiren/hydrochlorothiazide (300/25 mg) and 29.2/16.4 mmHg for amlodipine/hydrochlorothiazide (10/25 mg) (the subset constitutes patients without aberrant readings, defined as a difference between systolic blood pressure (SBP) readings ≥10 mmHg at baseline or endpoint). The effect of Rasitrio was observed as early as one week after initiation of therapy. The blood-pressure-lowering effect in patients with moderate to severe hypertension was independent of age, gender, race, body mass index and overweight-associated disorders (metabolic syndrome and diabetes).

Rasitrio was associated with a significant reduction in plasma renin activity (PRA) (-34%) from baseline while the dual combination of amlodipine with hydrochlorothiazide increased PRA (+170%). The clinical implications of the differences in effect on PRA are not known at the present time.

In a 28 to 54 week open label safety study, efficacy was measured as secondary endpoint and Rasitrio at a dose of 300/10/25 mg produced mean blood pressure reductions (systolic/diastolic) of 37.3/21.8 mmHg over 28 to 54 weeks of treatment. Efficacy of Rasitrio was maintained over one year of treatment, with no evidence of loss of effect.

In a randomised, double blind, active controlled, 36-week study in elderly patients whose blood pressure was not controlled with aliskiren/HCTZ 300/25 mg (SBP ≥140 mmHg), clinically meaningful further BP reduction was seen at week 36 endpoint for patients who received Rasitrio at a dose of 300/10/25 mg (from reductions in msSBP/msDBP of 15.0/8.6 mmHg at week 22 to reductions of 30.8/14.1 mmHg at week 36 endpoint).

Rasitrio has been administered to more than 1,155 patients in completed clinical trials, including 182 patients for one year or more. Treatment with Rasitrio was well tolerated at doses up to 300 mg/10 mg/25 mg with an overall incidence of adverse events similar to the corresponding dual combinations, except for symptomatic hypotension. The incidence of any adverse reactions potentially related to hypotension in a short-term controlled study was 4.9% with Rasitrio versus up to 3.7% with dual combinations. In patients ≥65 years the incidence was 10.2% with Rasitrio versus up to 5.4% with dual combinations.

The incidence of adverse events did not show any association with gender, age (with the exception of symptomatic hypotension), body mass index, race or ethnicity. Adverse events have generally been mild and transient in nature. Very limited safety data are available for patients aged >75 years or patients with major cardiovascular co-morbidities. Discontinuation of therapy due to a clinical adverse event occurred in 3.6% of patients treated with Rasitrio versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/hydrochlorothiazide and 2.7% in amlodipine/hydrochlorothiazide.

Aliskiren

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other medicinal products that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive medicinal products. The clinical implications of the differences in effect on PRA are not known at the present time.

Hypertension

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood-pressure-lowering effects comparable to other classes of antihypertensive medicinal products including selected ACEI and ARB. Compared to a diuretic (hydrochlorothiazide, HCTZ), aliskiren 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Aliskiren induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide.

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (≥65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12-week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the dosages chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In an 8-week study in 754 hypertensive geriatric patients aged 65 years or older and geriatric patients aged 75 years or older (30%) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive medicinal products. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular remodelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR <60 ml/min/1.73 m^2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. Study results indicated a hazard ratio for the primary endpoint of 1.11 in favour of placebo (95% Confidence Interval: 1.00, 1.23, 2-sided p=0.05). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (37.9% versus 30.2%). In particular there was an increased incidence of renal dysfunction (14.0% versus 12.1%), hyperkalaemia (38.9% versus 28.8%), hypotension-related events (19.7% versus 16.2%) and adjudicated stroke endpoints (3.4% versus 2.6%). The increased incidence of stroke was greater in patients with renal insufficiency.

Effects of aliskiren on mortality and cardiovascular morbidity are currently unknown.

No long-term efficacy data for aliskiren in patients with heart failure are currently available (see section 4.4).

Cardiac electrophysiology
No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Amlodipine
The amlodipine component of Rasitrio inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites.

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Use in patients with heart failure
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasitrio in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Aliskiren/amlodipine/hydrochlorothiazide combination
Following oral administration of a fixed combination tablet of aliskiren, amlodipine and hydrochlorothiazide, peak concentrations were achieved for aliskiren within 1-2 hours, for amlodipine within 8 hours and for hydrochlorothiazide within 2-3 hours. The rate and extent of absorption of aliskiren, amlodipine and hydrochlorothiazide following administration of a fixed combination tablet are similar to when administered as individual dosage forms.

The results from a food effect study using a standard high-fat meal with the 300/10/25 mg fixed combination tablet showed that food reduced the rate and extent of absorption of aliskiren in the fixed combination tablet with a similar magnitude of effect as for aliskiren monotherapy. Food had no effect on the pharmacokinetics of amlodipine or hydrochlorothiazide in the fixed combination tablet.

Aliskiren
Absorption
Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and AUC $_{0-tau}$ by 67% in hypertensive patients. Steady-state plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution
Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation and elimination
The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C_{max}, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients (aged 6-17 years) given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The available data did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

<u>Amlodipine</u>
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution
The volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation and elimination
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days.

Linearity
Amlodipine exhibits linear pharmacokinetics between the therapeutic dose range of 5 mg and 10 mg.

<u>Hydrochlorothiazide</u>
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution
The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation and elimination
Hydrochlorothiazide is eliminated predominantly as unchanged compound. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Linearity
The increase in mean AUC is linear and dose proportional in the therapeutic range.

Special populations
Rasitrio is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

Renal impairment
Due to its hydrochlorothiazide component, Rasitrio is contraindicated in patients with anuria or severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.3). No adjustment of the initial dose is required in patients with mild to moderate renal impairment (see sections 4.4 and 4.2).

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and C_{max} of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dose of aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2). Concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with renal impairment (GFR <60 ml/min/1.73 m^2) (see section 4.3).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in C_{max} of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide. In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Hepatic impairment
Rasitrio is contraindicated in patients with severe hepatic impairment (see section 4.3).

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to moderate hepatic impairment.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. Therefore caution should be exercised in patients with hepatic impairment.

Geriatric patients
No data are available on systemic exposure after administration of Rasitrio in geriatric patients. When administered alone, the AUC of aliskiren in geriatric subjects (>65 years) is 50% higher than in young subjects. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in geriatric patients. Therefore particular caution is recommended when administering Rasitrio to patients aged 65 years and over, and extreme caution in patients aged 75 years or older (see sections 4.2, 4.4, 4.8 and 5.1).

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. There are no specific data regarding the effect of hydrochlorothiazide in elderly patients.

Paediatric population (age below 18 years)
The pharmacokinetics of Rasitrio have not been investigated. A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

5.3 Preclinical safety data

Aliskiren/hydrochlorothiazide and aliskiren/amlodipine
Non-clinical studies of the toxicology of Rasitrio alone have not been conducted as these studies have been conducted for the individual components.

The toxicity profiles of the combination of aliskiren/hydrochlorothiazide and aliskiren/amlodipine have been well characterised in preclinical studies. Both combinations were generally well tolerated by rats. The findings from 2- and 13-week oral toxicity studies were consistent with those for the individual components.

Aliskiren
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1,500 mg/kg/day were not statistically significant. Although aliskiren has known irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The assays included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local irritation potential or the expected pharmacological effects of aliskiren.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically.

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25 and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no effects related to the medicinal product at either the gene or chromosome levels.

*Based on patient weight of 50 kg

Hydrochlorothiazide

Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg,/day respectively, prior to mating and throughout gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)
Iron oxide black (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/polychlorotrifluoroethylene (PCTFE) – Alu calendar blisters:
2 years

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
2 years

PA/Alu/PVC – Alu calendar blisters:
18 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets

PVC/polychlorotrifluoroethylene (PCTFE) - Alu blisters:
Single pack containing 30, 90 tablets
Unit dose pack (perforated unit dose blister) containing 56x1 tablet
Multipacks of unit dose (perforated unit dose blister) containing 98x1 tablet (2 packs of 49x1)

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multipacks containing 98 tablets (2 packs of 49)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/049-060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Novartis Farma S.p.A.
Via Provinciale Schito 131
IT-80058 Torre Annunziata
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The MAH shall submit the final study report of the ALTITUDE study, including the 1-year safety extension phase covering the results of the active treatment phase relevant to the two different cut-off dates.	31 October 2013

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/001	14 tablets (PVC/PCTFE blisters)
EU/1/11/730/009	14 tablets (PA/Alu/PVC blisters)
EU/1/11/730/002	28 tablets (PVC/PCTFE blisters)
EU/1/11/730/010	28 tablets (PA/Alu/PVC blisters)
EU/1/11/730/003	30 tablets (PVC/PCTFE blisters)
EU/1/11/730/004	56 tablets (PVC/PCTFE blisters)
EU/1/11/730/011	56 tablets (PA/Alu/PVC blisters)
EU/1/11/730/007	56 tablets (PVC/PCTFE single-unit-dose blisters)
EU/1/11/730/005	90 tablets (PVC/PCTFE blisters)
EU/1/11/730/006	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 150 mg/5 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.

Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/012 98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/008 98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 150 mg/5 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 98 (2 packs of 49x1) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/012	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/008	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 150 mg/5 mg/12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (CALENDAR) (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/013	14 tablets (PVC/PCTFE blisters)
EU/1/11/730/021	14 tablets (PA/Alu/PVC blisters)
EU/1/11/730/014	28 tablets (PVC/PCTFE blisters)
EU/1/11/730/022	28 tablets (PA/Alu/PVC blisters)
EU/1/11/730/015	30 tablets (PVC/PCTFE blisters)
EU/1/11/730/016	56 tablets (PVC/PCTFE blisters)
EU/1/11/730/023	56 tablets (PA/Alu/PVC blisters)
EU/1/11/730/019	56 tablets (PVC/PCTFE single-unit-dose blisters)
EU/1/11/730/017	90 tablets (PVC/PCTFE blisters)
EU/1/11/730/018	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.

Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/024 98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/020 98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 98 (2 packs of 49x1) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/024 98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/020 98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (CALENDAR) (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/025	14 tablets (PVC/PCTFE blisters)
EU/1/11/730/033	14 tablets (PA/Alu/PVC blisters)
EU/1/11/730/026	28 tablets (PVC/PCTFE blisters)
EU/1/11/730/034	28 tablets (PA/Alu/PVC blisters)
EU/1/11/730/027	30 tablets (PVC/PCTFE blisters)
EU/1/11/730/028	56 tablets (PVC/PCTFE blisters)
EU/1/11/730/035	56 tablets (PA/Alu/PVC blisters)
EU/1/11/730/031	56 tablets (PVC/PCTFE single-unit-dose blisters)
EU/1/11/730/029	90 tablets (PVC/PCTFE blisters)
EU/1/11/730/030	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.

Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/036	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/032	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 5 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 98 (2 packs of 49x1) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/036	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/032	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/5 mg/25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (CALENDAR) (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/037	14 tablets (PVC/PCTFE blisters)
EU/1/11/730/045	14 tablets (PA/Alu/PVC blisters)
EU/1/11/730/038	28 tablets (PVC/PCTFE blisters)
EU/1/11/730/046	28 tablets (PA/Alu/PVC blisters)
EU/1/11/730/039	30 tablets (PVC/PCTFE blisters)
EU/1/11/730/040	56 tablets (PVC/PCTFE blisters)
EU/1/11/730/047	56 tablets (PA/Alu/PVC blisters)
EU/1/11/730/043	56 tablets (PVC/PCTFE single-unit-dose blisters)
EU/1/11/730/041	90 tablets (PVC/PCTFE blisters)
EU/1/11/730/042	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.

Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/048	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/044	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/12.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 98 (2 packs of 49x1) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/048	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/044	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/12.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (CALENDAR) (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/049	14 tablets (PVC/PCTFE blisters)
EU/1/11/730/057	14 tablets (PA/Alu/PVC blisters)
EU/1/11/730/050	28 tablets (PVC/PCTFE blisters)
EU/1/11/730/058	28 tablets (PA/Alu/PVC blisters)
EU/1/11/730/051	30 tablets (PVC/PCTFE blisters)
EU/1/11/730/052	56 tablets (PVC/PCTFE blisters)
EU/1/11/730/059	56 tablets (PA/Alu/PVC blisters)
EU/1/11/730/055	56 tablets (PVC/PCTFE single-unit-dose blisters)
EU/1/11/730/053	90 tablets (PVC/PCTFE blisters)
EU/1/11/730/054	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.

Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/060 98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/056 98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK OF 98 (2 packs of 49 film-coated tablets) - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate), 10 mg amlodipine (as amlodipine besylate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 98 (2 packs of 49x1) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/730/060	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/730/056	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasitrio 300 mg/10 mg/25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (CALENDAR) (PVC/PCTFE OR PA/Alu/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

B. PACKAGE LEAFLET

Package leaflet: information for the user

Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Rasitrio is and what it is used for

What Rasitrio is
Rasitrio contains three active substances, called aliskiren, amlodipine and hydrochlorothiazide. All of these substances help to control high blood pressure (hypertension).

– Aliskiren is a substance that belongs to a group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.
– Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax; this lowers blood pressure.
– Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

What Rasitrio is used for
Rasitrio is used to treat high blood pressure in adult patients who have their blood pressure already controlled by aliskiren, amlodipine and hydrochlorothiazide taken as separate medicines given at the same time. These patients may thus benefit from taking one tablet containing all three substances.

2. What you need to know before you take Rasitrio

Do not take Rasitrio
- if you are allergic to aliskiren, to amlodipine, to other dihydropyridine-derived medicines (known as calcium channel blockers), to hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, do not take Rasitrio and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren,
  - hereditary angioedema,
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Rasitrio in early pregnancy – see Pregnancy section).
- if you have serious liver problems.
- if you have serious kidney problems.
- if you have problems to produce urine (anuria).
- if the level of potassium in your blood is too low despite treatment.
- if the level of sodium in your blood is too low.
- if the level of calcium in your blood is too high.
- if you have gout (uric acid crystals in the joints).
- if you are taking any of the following medicines:
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis),
  - itraconazole (a medicine used to treat fungal infections),
  - quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you have a very low blood pressure.
- if you are suffering from shock, including cardiogenic shock.
- if you have a narrowing of the aortic heart valve (aortic stenosis).
- if you have heart failure after an acute heart attack.

If any of the above applies to you, do not take Rasitrio and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Rasitrio:
- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce).
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasitrio and contact your doctor.
- if you suffer from heart problems.
- if you are on a low-salt diet.
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis), including if you have had a kidney transplant or a narrowing or blockage of the arteries that supply blood to your kidney.
- if you have impaired kidney function, your doctor will carefully consider whether Rasitrio is suitable for you and may wish to monitor you carefully.
- if you suffer from liver problems (impaired liver function).
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").

- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.
- if you are 65 years of age or older (see section Elderly (age 65 years or older) below).
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, restlessness, muscle pain or cramps, weakness, low blood pressure, reduced urine output, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Rasitrio).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Rasitrio. This can lead to permanent vision impairment, if not treated.
- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body.

You must tell your doctor if you think you are (or might become) pregnant. Rasitrio is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

Children and adolescents
The use of Rasitrio in children and adolescents up to 18 years of age is not recommended.

Elderly
You should tell your doctor if you are 65 years of age or older because you may be more susceptible to side effects related to low blood pressure (see section 4 on possible side effects). Your doctor will carefully consider whether Rasitrio is suitable for you. If you are 75 years of age or older, your doctor may wish to monitor your blood pressure more frequently.

In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasitrio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Rasitrio and talk to your doctor if you are taking any of the following medicines:
- ciclosporin (a medicine used in transplantation to prevent organ rejection and also in other conditions, e.g. rheumatoid arthritis or atopic dermatitis).
- itraconazole (a medicine used to treat fungal infections).
- quinidine (a medicine used to correct heart rhythm).
- one of the following classes of medicines used to treat high blood pressure if you have diabetes mellitus or impaired kidney function:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.

Tell your doctor if you are using the following medicines:
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- medicines that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- ketonazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections.
- amiodarone, a medicine used to treat abnormal heart rhythms.
- atorvastatin, a medicine used to treat high cholesterol.
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- rifampicin, a medicine used to prevent or treat infections.
- St. John's wort *(hypericum perforatum)*, a herbal medicine used to elevate mood.
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors) (used especially in the patients over 65 years old).
- diltiazem, a medicine used to treat heart problems.
- ritonavir, a medicine used to treat viral infection.
- lithium (a medicine used to treat some types of depression).
- some laxatives.
- medicines for the treatment of gout, such as allopurinol.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- one of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- medicines used to control heart rhythm.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- steroids.
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- arthritis medicines.
- medicines used to treat oesophageal ulceration and inflammation (e.g. carbenoxolone).
- muscle relaxants (medicines to relax the muscles which are used during operations).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- some medicines used to treat infections, such as ketoconazole, amphotericin or penicillin G.

Rasitrio with food and drink
You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine with grapefruit juice.

Due to hydrochlorothiazide contained in Rasitrio, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially when getting up from a sitting position.

Pregnancy
Do not take this medicine if you are pregnant (see section Do not take Rasitrio). If you become pregnant while taking this medicine stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking Rasitrio before you become pregnant and will advise you to take another medicine instead of Rasitrio. Rasitrio is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasitrio is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
This medicine may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasitrio

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasitrio is one tablet a day.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine together with grapefruit juice.

If you take more Rasitrio than you should
If you have accidentally taken too many Rasitrio tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasitrio
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported for Rasitrio are:
Common *(may affect up to 1 in 10 people)*
- dizziness
- low blood pressure
- swelling of hands, ankles and feet (peripheral oedema).

Tell your doctor immediately if you experience the following at the beginning of your treatment:
Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasitrio. Patients 65 years of age or older are more susceptible to side effects related to low blood pressure. In clinical trials low blood pressure occurred more frequently in patients taking Rasitrio than those taking only dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide (see section 2).

The following, possibly serious, side effects have been reported with medicines containing aliskiren, amlodipine or hydrochlorothiazide alone.

Aliskiren
Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder).

Possible side effects
Common *(may affect up to 1 in 10 people)*
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness.

Uncommon *(may affect up to 1 in 100 people)*
- skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- kidney problems including acute renal failure (severely decreased urine output)
- swelling of hands, ankles or feet (peripheral oedema)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions – red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- low blood pressure

- palpitations
- cough
- itching, itchy rash (urticaria)
- increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*
- severe allergic reaction (anaphylactic reaction)
- allergic reactions (hypersensitivity)
- angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- increased level of creatinine in the blood
- red skin (erythema).

Amlodipine
In patients taking amlodipine alone, the following have been reported:
Common *(may affect up to 1 in 10 people)*
- sleepiness
- dizziness
- headache (especially at the beginning of treatment)
- hot flushes
- abdominal pain
- nausea
- ankle swelling
- swelling
- tiredness
- palpitations (awareness of your heart beat).

Uncommon *(may affect up to 1 in 100 people)*
- insomnia
- mood changes (including anxiety)
- depression
- trembling
- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- low blood pressure
- breathlessness
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration
- excessive sweating
- itching; rash
- generalised rash
- joint pain
- muscle pain
- muscle cramps
- back pain
- urination disorders

- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease.

Rare *(may affect up to 1 in 1,000 people)*
- confusion.

Very rare *(may affect up to 1 in 10,000 people)*
- low level of white blood cells and blood platelets
- allergic reaction with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- cough
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver
- liver disorder which can occur together with yellow skin and eyes, or dark-coloured urine
- abnormal liver function test
- angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue)
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth; dry skin, rash, itchy rash
- skin rash with flaking or peeling; rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun.

<u>Hydrochlorothiazide</u>
In patients taking hydrochlorothiazide alone, the following have been reported, however the frequency cannot be estimated from the available data:
Very common *(may affect more than 1 in 10 people)*
- low level of potassium in the blood
- increase of lipids in the blood.

Common *(may affect up to 1 in 10 people)*
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection.

Rare *(may affect up to 1 in 1,000 people)*
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- high level of calcium in the blood
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- sad mood (depression)
- sleep disturbances
- dizziness
- headache
- tingling or numbness
- vision disorder
- irregular heart beat
- abdominal discomfort
- constipation
- diarrhoea
- liver disorders which can occur together with yellow skin and eyes
- increased sensitivity of skin to the sun
- sugar in the urine.

Very rare *(may affect up to 1 in 10,000 people)*
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- severe upper stomach pain (pancreatitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis).

Not known *(frequency cannot be estimated from the available data)*
- weakness
- bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- fever.

If any of these affect you severely, tell your doctor. You may need to stop Rasitrio.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Rasitrio

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
Do not store above 30°C.
Store Rasitrio tablets in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasitrio contains
- Each Rasitrio 150 mg/5 mg/12.5 mg film-coated tablet contains 150 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide. The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide red (E172), iron oxide black (E172).

What Rasitrio looks like and contents of the pack
- Rasitrio 150 mg/5 mg/12.5 mg film-coated tablets are violet white, oval tablets, with "YIY" debossed on one side and "NVR" on the other.

Rasitrio is available in packs containing 14, 28, 56, 98 tablets in calendar blisters.
It is also available in multi-packs of 98 tablets (2 packs of 49) in calendar blisters.

Rasitrio is available in packs containing 30 or 90 tablets in blisters.
Rasitrio is available in packs containing 56x1 tablet in perforated unit dose blister.
It is also available in multi-packs of 98x1 tablet (2 packs of 49x1) in perforated unit dose blister.

Not all pack sizes may be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Package leaflet: information for the user

Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Rasitrio is and what it is used for

What Rasitrio is
Rasitrio contains three active substances, called aliskiren, amlodipine and hydrochlorothiazide. All of these substances help to control high blood pressure (hypertension).

– Aliskiren is a substance that belongs to a group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.
– Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax; this lowers blood pressure.
– Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

What Rasitrio is used for
Rasitrio is used to treat high blood pressure in adult patients who have their blood pressure already controlled by aliskiren, amlodipine and hydrochlorothiazide taken as separate medicines given at the same time. These patients may thus benefit from taking one tablet containing all three substances.

2. What you need to know before you take Rasitrio

Do not take Rasitrio
- if you are allergic to aliskiren, to amlodipine, to other dihydropyridine-derived medicines (known as calcium channel blockers), to hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, do not take Rasitrio and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren,
  - hereditary angioedema,
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Rasitrio in early pregnancy – see Pregnancy section).
- if you have serious liver problems.
- if you have serious kidney problems.
- if you have problems to produce urine (anuria).
- if the level of potassium in your blood is too low despite treatment.
- if the level of sodium in your blood is too low.
- if the level of calcium in your blood is too high.
- if you have gout (uric acid crystals in the joints).
- if you are taking any of the following medicines:
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis),
  - itraconazole (a medicine used to treat fungal infections),
  - quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you have a very low blood pressure.
- if you are suffering from shock, including cardiogenic shock.
- if you have a narrowing of the aortic heart valve (aortic stenosis).
- if you have heart failure after an acute heart attack.

If any of the above applies to you, do not take Rasitrio and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Rasitrio:
- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce).
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasitrio and contact your doctor.
- if you suffer from heart problems.
- if you are on a low-salt diet.
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis), including if you have had a kidney transplant or a narrowing or blockage of the arteries that supply blood to your kidney.
- if you have impaired kidney function, your doctor will carefully consider whether Rasitrio is suitable for you and may wish to monitor you carefully.
- if you suffer from liver problems (impaired liver function).
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").

- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.
- if you are 65 years of age or older (see section Elderly (age 65 years or older) below).
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, restlessness, muscle pain or cramps, weakness, low blood pressure, reduced urine output, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Rasitrio).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Rasitrio. This can lead to permanent vision impairment, if not treated.
- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body.

You must tell your doctor if you think you are (or might become) pregnant. Rasitrio is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

Children and adolescents
The use of Rasitrio in children and adolescents up to 18 years of age is not recommended.

Elderly
You should tell your doctor if you are 65 years of age or older because you may be more susceptible to side effects related to low blood pressure (see section 4 on possible side effects). Your doctor will carefully consider whether Rasitrio is suitable for you. If you are 75 years of age or older, your doctor may wish to monitor your blood pressure more frequently.

In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasitrio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Rasitrio and talk to your doctor if you are taking any of the following medicines:
- ciclosporin (a medicine used in transplantation to prevent organ rejection and also in other conditions, e.g. rheumatoid arthritis or atopic dermatitis).
- itraconazole (a medicine used to treat fungal infections).
- quinidine (a medicine used to correct heart rhythm).
- one of the following classes of medicines used to treat high blood pressure if you have diabetes mellitus or impaired kidney function:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.

Tell your doctor if you are using the following medicines:
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- medicines that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- ketonazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections.
- amiodarone, a medicine used to treat abnormal heart rhythms.
- atorvastatin, a medicine used to treat high cholesterol.
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- rifampicin, a medicine used to prevent or treat infections.
- St. John's wort *(hypericum perforatum)*, a herbal medicine used to elevate mood.
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors) (used especially in the patients over 65 years old).
- diltiazem, a medicine used to treat heart problems.
- ritonavir, a medicine used to treat viral infection.
- lithium (a medicine used to treat some types of depression).
- some laxatives.
- medicines for the treatment of gout, such as allopurinol.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- one of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- medicines used to control heart rhythm.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- steroids.
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- arthritis medicines.
- medicines used to treat oesophageal ulceration and inflammation (e.g. carbenoxolone).
- muscle relaxants (medicines to relax the muscles which are used during operations).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- some medicines used to treat infections, such as ketoconazole, amphotericin or penicillin G.

Rasitrio with food and drink
You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine with grapefruit juice.

Due to hydrochlorothiazide contained in Rasitrio, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially when getting up from a sitting position.

Pregnancy
Do not take this medicine if you are pregnant (see section Do not take Rasitrio). If you become pregnant while taking this medicine stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking Rasitrio before you become pregnant and will advise you to take another medicine instead of Rasitrio. Rasitrio is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasitrio is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
This medicine may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasitrio

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasitrio is one tablet a day.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine together with grapefruit juice.

If you take more Rasitrio than you should
If you have accidentally taken too many Rasitrio tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasitrio
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported for Rasitrio are:
Common *(may affect up to 1 in 10 people)*
- dizziness
- low blood pressure
- swelling of hands, ankles and feet (peripheral oedema).

Tell your doctor immediately if you experience the following at the beginning of your treatment:
Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasitrio. Patients 65 years of age or older are more susceptible to side effects related to low blood pressure. In clinical trials low blood pressure occurred more frequently in patients taking Rasitrio than those taking only dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide (see section 2).

The following, possibly serious, side effects have been reported with medicines containing aliskiren, amlodipine or hydrochlorothiazide alone.

Aliskiren
Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder).

Possible side effects
Common *(may affect up to 1 in 10 people)*
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness.

Uncommon *(may affect up to 1 in 100 people)*
- skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- kidney problems including acute renal failure (severely decreased urine output)
- swelling of hands, ankles or feet (peripheral oedema)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions – red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- low blood pressure
- palpitations
- cough
- itching, itchy rash (urticaria)
- increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*
- severe allergic reaction (anaphylactic reaction)
- allergic reactions (hypersensitivity)
- angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- increased level of creatinine in the blood
- red skin (erythema).

Amlodipine
In patients taking amlodipine alone, the following have been reported:
Common *(may affect up to 1 in 10 people)*
- sleepiness
- dizziness
- headache (especially at the beginning of treatment)
- hot flushes
- abdominal pain
- nausea
- ankle swelling
- swelling
- tiredness
- palpitations (awareness of your heart beat).

Uncommon *(may affect up to 1 in 100 people)*
- insomnia
- mood changes (including anxiety)
- depression
- trembling
- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- low blood pressure
- breathlessness
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration

- excessive sweating
- itching; rash
- generalised rash
- joint pain
- muscle pain
- muscle cramps
- back pain
- urination disorders
- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease.

Rare *(may affect up to 1 in 1,000 people)*
- confusion.

Very rare *(may affect up to 1 in 10,000 people)*
- low level of white blood cells and blood platelets
- allergic reaction with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- cough
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver
- liver disorder which can occur together with yellow skin and eyes, or dark-coloured urine
- abnormal liver function test
- angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue)
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth; dry skin, rash, itchy rash
- skin rash with flaking or peeling; rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun.

<u>Hydrochlorothiazide</u>
In patients taking hydrochlorothiazide alone, the following have been reported, however the frequency cannot be estimated from the available data:
Very common *(may affect more than 1 in 10 people)*
- low level of potassium in the blood
- increase of lipids in the blood.

Common *(may affect up to 1 in 10 people)*
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection.

Rare *(may affect up to 1 in 1,000 people)*
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- high level of calcium in the blood
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- sad mood (depression)
- sleep disturbances
- dizziness
- headache
- tingling or numbness
- vision disorder
- irregular heart beat
- abdominal discomfort
- constipation
- diarrhoea
- liver disorders which can occur together with yellow skin and eyes
- increased sensitivity of skin to the sun
- sugar in the urine.

Very rare *(may affect up to 1 in 10,000 people)*
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- severe upper stomach pain (pancreatitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis).

Not known *(frequency cannot be estimated from the available data)*
- weakness
- bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- fever.

If any of these affect you severely, tell your doctor. You may need to stop Rasitrio.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Rasitrio

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
Do not store above 30°C.
Store Rasitrio tablets in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasitrio contains
- Each Rasitrio 300 mg/5 mg/12.5 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide. The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide red (E172), iron oxide black (E172).

What Rasitrio looks like and contents of the pack
- Rasitrio 300 mg/5 mg/12.5 mg film-coated tablets are light pink, oval tablets, with "LIL" debossed on one side and "NVR" on the other.

Rasitrio is available in packs containing 14, 28, 56, 98 tablets in calendar blisters.
It is also available in multi-packs of 98 tablets (2 packs of 49) in calendar blisters.

Rasitrio is available in packs containing 30 or 90 tablets in blisters.
Rasitrio is available in packs containing 56x1 tablet in perforated unit dose blister.
It is also available in multi-packs of 98x1 tablet (2 packs of 49x1) in perforated unit dose blister.

Not all pack sizes may be available in your country.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Package leaflet: information for the user

Rasitrio 300 mg/5 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Rasitrio is and what it is used for

What Rasitrio is
Rasitrio contains three active substances, called aliskiren, amlodipine and hydrochlorothiazide. All of these substances help to control high blood pressure (hypertension).

– Aliskiren is a substance that belongs to a group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.
– Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax; this lowers blood pressure.
– Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

What Rasitrio is used for
Rasitrio is used to treat high blood pressure in adult patients who have their blood pressure already controlled by aliskiren, amlodipine and hydrochlorothiazide taken as separate medicines given at the same time. These patients may thus benefit from taking one tablet containing all three substances.

2. What you need to know before you take Rasitrio

Do not take Rasitrio
- if you are allergic to aliskiren, to amlodipine, to other dihydropyridine-derived medicines (known as calcium channel blockers), to hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, do not take Rasitrio and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren,
  - hereditary angioedema,
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Rasitrio in early pregnancy – see Pregnancy section).
- if you have serious liver problems.
- if you have serious kidney problems.
- if you have problems to produce urine (anuria).
- if the level of potassium in your blood is too low despite treatment.
- if the level of sodium in your blood is too low.
- if the level of calcium in your blood is too high.
- if you have gout (uric acid crystals in the joints).
- if you are taking any of the following medicines:
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis),
  - itraconazole (a medicine used to treat fungal infections),
  - quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you have a very low blood pressure.
- if you are suffering from shock, including cardiogenic shock.
- if you have a narrowing of the aortic heart valve (aortic stenosis).
- if you have heart failure after an acute heart attack.

If any of the above applies to you, do not take Rasitrio and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Rasitrio:
- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce).
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasitrio and contact your doctor.
- if you suffer from heart problems.
- if you are on a low-salt diet.
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis), including if you have had a kidney transplant or a narrowing or blockage of the arteries that supply blood to your kidney.
- if you have impaired kidney function, your doctor will carefully consider whether Rasitrio is suitable for you and may wish to monitor you carefully.
- if you suffer from liver problems (impaired liver function).
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").

- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.
- if you are 65 years of age or older (see section Elderly (age 65 years or older) below).
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, restlessness, muscle pain or cramps, weakness, low blood pressure, reduced urine output, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Rasitrio).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Rasitrio. This can lead to permanent vision impairment, if not treated.
- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body.

You must tell your doctor if you think you are (or might become) pregnant. Rasitrio is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

Children and adolescents
The use of Rasitrio in children and adolescents up to 18 years of age is not recommended.

Elderly
You should tell your doctor if you are 65 years of age or older because you may be more susceptible to side effects related to low blood pressure (see section 4 on possible side effects). Your doctor will carefully consider whether Rasitrio is suitable for you. If you are 75 years of age or older, your doctor may wish to monitor your blood pressure more frequently.

In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasitrio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Rasitrio and talk to your doctor if you are taking any of the following medicines:
- ciclosporin (a medicine used in transplantation to prevent organ rejection and also in other conditions, e.g. rheumatoid arthritis or atopic dermatitis).
- itraconazole (a medicine used to treat fungal infections).
- quinidine (a medicine used to correct heart rhythm).
- one of the following classes of medicines used to treat high blood pressure if you have diabetes mellitus or impaired kidney function:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.

Tell your doctor if you are using the following medicines:
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- medicines that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- ketonazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections.
- amiodarone, a medicine used to treat abnormal heart rhythms.
- atorvastatin, a medicine used to treat high cholesterol.
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- rifampicin, a medicine used to prevent or treat infections.
- St. John's wort *(hypericum perforatum)*, a herbal medicine used to elevate mood.
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors) (used especially in the patients over 65 years old).
- diltiazem, a medicine used to treat heart problems.
- ritonavir, a medicine used to treat viral infection.
- lithium (a medicine used to treat some types of depression).
- some laxatives.
- medicines for the treatment of gout, such as allopurinol.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- one of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- medicines used to control heart rhythm.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- steroids.
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- arthritis medicines.
- medicines used to treat oesophageal ulceration and inflammation (e.g. carbenoxolone).
- muscle relaxants (medicines to relax the muscles which are used during operations).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- some medicines used to treat infections, such as ketoconazole, amphotericin or penicillin G.

Rasitrio with food and drink
You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine with grapefruit juice.

Due to hydrochlorothiazide contained in Rasitrio, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially when getting up from a sitting position.

Pregnancy
Do not take this medicine if you are pregnant (see section Do not take Rasitrio). If you become pregnant while taking this medicine stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking Rasitrio before you become pregnant and will advise you to take another medicine instead of Rasitrio. Rasitrio is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasitrio is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
This medicine may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasitrio

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasitrio is one tablet a day.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine together with grapefruit juice.

If you take more Rasitrio than you should
If you have accidentally taken too many Rasitrio tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasitrio
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported for Rasitrio are:
Common *(may affect up to 1 in 10 people)*
- dizziness
- low blood pressure
- swelling of hands, ankles and feet (peripheral oedema).

Tell your doctor immediately if you experience the following at the beginning of your treatment:
Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasitrio. Patients 65 years of age or older are more susceptible to side effects related to low blood pressure. In clinical trials low blood pressure occurred more frequently in patients taking Rasitrio than those taking only dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide (see section 2).

The following, possibly serious, side effects have been reported with medicines containing aliskiren, amlodipine or hydrochlorothiazide alone.

Aliskiren
Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder).

Possible side effects
Common *(may affect up to 1 in 10 people)*
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness.

Uncommon *(may affect up to 1 in 100 people)*
- skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- kidney problems including acute renal failure (severely decreased urine output)
- swelling of hands, ankles or feet (peripheral oedema)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions – red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- low blood pressure
- palpitations
- cough
- itching, itchy rash (urticaria)
- increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*
- severe allergic reaction (anaphylactic reaction)
- allergic reactions (hypersensitivity)
- angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- increased level of creatinine in the blood
- red skin (erythema).

Amlodipine
In patients taking amlodipine alone, the following have been reported:
Common *(may affect up to 1 in 10 people)*
- sleepiness
- dizziness
- headache (especially at the beginning of treatment)
- hot flushes
- abdominal pain
- nausea
- ankle swelling
- swelling
- tiredness
- palpitations (awareness of your heart beat).

Uncommon *(may affect up to 1 in 100 people)*
- insomnia
- mood changes (including anxiety)
- depression
- trembling
- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- low blood pressure
- breathlessness
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration

- excessive sweating
- itching; rash
- generalised rash
- joint pain
- muscle pain
- muscle cramps
- back pain
- urination disorders
- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease.

Rare *(may affect up to 1 in 1,000 people)*
- confusion.

Very rare *(may affect up to 1 in 10,000 people)*
- low level of white blood cells and blood platelets
- allergic reaction with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- cough
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver
- liver disorder which can occur together with yellow skin and eyes, or dark-coloured urine
- abnormal liver function test
- angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue)
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth; dry skin, rash, itchy rash
- skin rash with flaking or peeling; rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun.

<u>Hydrochlorothiazide</u>
In patients taking hydrochlorothiazide alone, the following have been reported, however the frequency cannot be estimated from the available data:
Very common *(may affect more than 1 in 10 people)*
- low level of potassium in the blood
- increase of lipids in the blood.

Common *(may affect up to 1 in 10 people)*
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection.

Rare *(may affect up to 1 in 1,000 people)*
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- high level of calcium in the blood
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- sad mood (depression)
- sleep disturbances
- dizziness
- headache
- tingling or numbness
- vision disorder
- irregular heart beat
- abdominal discomfort
- constipation
- diarrhoea
- liver disorders which can occur together with yellow skin and eyes
- increased sensitivity of skin to the sun
- sugar in the urine.

Very rare *(may affect up to 1 in 10,000 people)*
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- severe upper stomach pain (pancreatitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis).

Not known *(frequency cannot be estimated from the available data)*
- weakness
- bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- fever.

If any of these affect you severely, tell your doctor. You may need to stop Rasitrio.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Rasitrio

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
Do not store above 30°C.
Store Rasitrio tablets in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasitrio contains
- Each Rasitrio 300 mg/5 mg/25 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate), 5 mg amlodipine (as besylate) and 25 mg hydrochlorothiazide. The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172).

What Rasitrio looks like and contents of the pack
- Rasitrio 300 mg/5 mg/25 mg film-coated tablets are pale orange-brown, oval tablets, with "OIO" debossed on one side and "NVR" on the other.

Rasitrio is available in packs containing 14, 28, 56, 98 tablets in calendar blisters.
It is also available in multi-packs of 98 tablets (2 packs of 49) in calendar blisters.

Rasitrio is available in packs containing 30 or 90 tablets in blisters.
Rasitrio is available in packs containing 56x1 tablet in perforated unit dose blister.
It is also available in multi-packs of 98x1 tablet (2 packs of 49x1) in perforated unit dose blister.

Not all pack sizes may be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Package leaflet: information for the user

Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Rasitrio is and what it is used for

What Rasitrio is
Rasitrio contains three active substances, called aliskiren, amlodipine and hydrochlorothiazide. All of these substances help to control high blood pressure (hypertension).

– Aliskiren is a substance that belongs to a group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.
– Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax; this lowers blood pressure.
– Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

What Rasitrio is used for
Rasitrio is used to treat high blood pressure in adult patients who have their blood pressure already controlled by aliskiren, amlodipine and hydrochlorothiazide taken as separate medicines given at the same time. These patients may thus benefit from taking one tablet containing all three substances.

2. What you need to know before you take Rasitrio

Do not take Rasitrio

- if you are allergic to aliskiren, to amlodipine, to other dihydropyridine-derived medicines (known as calcium channel blockers), to hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, do not take Rasitrio and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren,
  - hereditary angioedema,
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Rasitrio in early pregnancy – see Pregnancy section).
- if you have serious liver problems.
- if you have serious kidney problems.
- if you have problems to produce urine (anuria).
- if the level of potassium in your blood is too low despite treatment.
- if the level of sodium in your blood is too low.
- if the level of calcium in your blood is too high.
- if you have gout (uric acid crystals in the joints).
- if you are taking any of the following medicines:
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis),
  - itraconazole (a medicine used to treat fungal infections),
  - quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you have a very low blood pressure.
- if you are suffering from shock, including cardiogenic shock.
- if you have a narrowing of the aortic heart valve (aortic stenosis).
- if you have heart failure after an acute heart attack.

If any of the above applies to you, do not take Rasitrio and talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Rasitrio:

- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce).
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasitrio and contact your doctor.
- if you suffer from heart problems.
- if you are on a low-salt diet.
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis), including if you have had a kidney transplant or a narrowing or blockage of the arteries that supply blood to your kidney.
- if you have impaired kidney function, your doctor will carefully consider whether Rasitrio is suitable for you and may wish to monitor you carefully.
- if you suffer from liver problems (impaired liver function).
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").

- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.
- if you are 65 years of age or older (see section Elderly (age 65 years or older) below).
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, restlessness, muscle pain or cramps, weakness, low blood pressure, reduced urine output, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Rasitrio).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Rasitrio. This can lead to permanent vision impairment, if not treated.
- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body.

You must tell your doctor if you think you are (or might become) pregnant. Rasitrio is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

Children and adolescents
The use of Rasitrio in children and adolescents up to 18 years of age is not recommended.

Elderly
You should tell your doctor if you are 65 years of age or older because you may be more susceptible to side effects related to low blood pressure (see section 4 on possible side effects). Your doctor will carefully consider whether Rasitrio is suitable for you. If you are 75 years of age or older, your doctor may wish to monitor your blood pressure more frequently.

In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasitrio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Rasitrio and talk to your doctor if you are taking any of the following medicines:
- ciclosporin (a medicine used in transplantation to prevent organ rejection and also in other conditions, e.g. rheumatoid arthritis or atopic dermatitis).
- itraconazole (a medicine used to treat fungal infections).
- quinidine (a medicine used to correct heart rhythm).
- one of the following classes of medicines used to treat high blood pressure if you have diabetes mellitus or impaired kidney function:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.

Tell your doctor if you are using the following medicines:
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- medicines that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- ketonazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections.
- amiodarone, a medicine used to treat abnormal heart rhythms.
- atorvastatin, a medicine used to treat high cholesterol.
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- rifampicin, a medicine used to prevent or treat infections.
- St. John's wort *(hypericum perforatum)*, a herbal medicine used to elevate mood.
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors) (used especially in the patients over 65 years old).
- diltiazem, a medicine used to treat heart problems.
- ritonavir, a medicine used to treat viral infection.
- lithium (a medicine used to treat some types of depression).
- some laxatives.
- medicines for the treatment of gout, such as allopurinol.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- one of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- medicines used to control heart rhythm.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- steroids.
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- arthritis medicines.
- medicines used to treat oesophageal ulceration and inflammation (e.g. carbenoxolone).
- muscle relaxants (medicines to relax the muscles which are used during operations).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- some medicines used to treat infections, such as ketoconazole, amphotericin or penicillin G.

Rasitrio with food and drink
You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine with grapefruit juice.

Due to hydrochlorothiazide contained in Rasitrio, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially when getting up from a sitting position.

Pregnancy
Do not take this medicine if you are pregnant (see section Do not take Rasitrio). If you become pregnant while taking this medicine stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking Rasitrio before you become pregnant and will advise you to take another medicine instead of Rasitrio. Rasitrio is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasitrio is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
This medicine may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasitrio

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasitrio is one tablet a day.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine together with grapefruit juice.

If you take more Rasitrio than you should
If you have accidentally taken too many Rasitrio tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasitrio
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported for Rasitrio are:
Common *(may affect up to 1 in 10 people)*
- dizziness
- low blood pressure
- swelling of hands, ankles and feet (peripheral oedema).

Tell your doctor immediately if you experience the following at the beginning of your treatment:
Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasitrio. Patients 65 years of age or older are more susceptible to side effects related to low blood pressure. In clinical trials low blood pressure occurred more frequently in patients taking Rasitrio than those taking only dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide (see section 2).

The following, possibly serious, side effects have been reported with medicines containing aliskiren, amlodipine or hydrochlorothiazide alone.

Aliskiren
Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder).

Possible side effects
Common *(may affect up to 1 in 10 people)*
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness.

Uncommon *(may affect up to 1 in 100 people)*
- skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- kidney problems including acute renal failure (severely decreased urine output)
- swelling of hands, ankles or feet (peripheral oedema)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions – red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- low blood pressure
- palpitations
- cough
- itching, itchy rash (urticaria)
- increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*
- severe allergic reaction (anaphylactic reaction)
- allergic reactions (hypersensitivity)
- angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- increased level of creatinine in the blood
- red skin (erythema).

Amlodipine
In patients taking amlodipine alone, the following have been reported:
Common *(may affect up to 1 in 10 people)*
- sleepiness
- dizziness
- headache (especially at the beginning of treatment)
- hot flushes
- abdominal pain
- nausea
- ankle swelling
- swelling
- tiredness
- palpitations (awareness of your heart beat).

Uncommon *(may affect up to 1 in 100 people)*
- insomnia
- mood changes (including anxiety)
- depression
- trembling
- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- low blood pressure
- breathlessness
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration

- excessive sweating
- itching; rash
- generalised rash
- joint pain
- muscle pain
- muscle cramps
- back pain
- urination disorders
- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease.

Rare *(may affect up to 1 in 1,000 people)*
- confusion.

Very rare *(may affect up to 1 in 10,000 people)*
- low level of white blood cells and blood platelets
- allergic reaction with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- cough
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver
- liver disorder which can occur together with yellow skin and eyes, or dark-coloured urine
- abnormal liver function test
- angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue)
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth; dry skin, rash, itchy rash
- skin rash with flaking or peeling; rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun.

<u>Hydrochlorothiazide</u>
In patients taking hydrochlorothiazide alone, the following have been reported, however the frequency cannot be estimated from the available data:
Very common *(may affect more than 1 in 10 people)*
- low level of potassium in the blood
- increase of lipids in the blood.

Common *(may affect up to 1 in 10 people)*
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection.

Rare *(may affect up to 1 in 1,000 people)*
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- high level of calcium in the blood
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- sad mood (depression)
- sleep disturbances
- dizziness
- headache
- tingling or numbness
- vision disorder
- irregular heart beat
- abdominal discomfort
- constipation
- diarrhoea
- liver disorders which can occur together with yellow skin and eyes
- increased sensitivity of skin to the sun
- sugar in the urine.

Very rare *(may affect up to 1 in 10,000 people)*
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- severe upper stomach pain (pancreatitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis).

Not known *(frequency cannot be estimated from the available data)*
- weakness
- bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- fever.

If any of these affect you severely, tell your doctor. You may need to stop Rasitrio.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Rasitrio

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
Do not store above 30°C.
Store Rasitrio tablets in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasitrio contains
- Each Rasitrio 300 mg/10 mg/12.5 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate), 10 mg amlodipine (as besylate) and 12.5 mg hydrochlorothiazide. The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide red (E172), iron oxide black (E172).

What Rasitrio looks like and contents of the pack
- Rasitrio 300 mg/10 mg/12.5 mg film-coated tablets are light red, oval tablets, with "UIU" debossed on one side and "NVR" on the other.

Rasitrio is available in packs containing 14, 28, 56, 98 tablets in calendar blisters.
It is also available in multi-packs of 98 tablets (2 packs of 49) in calendar blisters.

Rasitrio is available in packs containing 30 or 90 tablets in blisters.
Rasitrio is available in packs containing 56x1 tablet in perforated unit dose blister.
It is also available in multi-packs of 98x1 tablet (2 packs of 49x1) in perforated unit dose blister.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Package leaflet: information for the user

Rasitrio 300 mg/10 mg/25 mg film-coated tablets
Aliskiren/amlodipine/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Rasitrio is and what it is used for

What Rasitrio is
Rasitrio contains three active substances, called aliskiren, amlodipine and hydrochlorothiazide. All of these substances help to control high blood pressure (hypertension).

– Aliskiren is a substance that belongs to a group of medicines called renin inhibitors. These reduce the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.
– Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax; this lowers blood pressure.
– Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

What Rasitrio is used for
Rasitrio is used to treat high blood pressure in adult patients who have their blood pressure already controlled by aliskiren, amlodipine and hydrochlorothiazide taken as separate medicines given at the same time. These patients may thus benefit from taking one tablet containing all three substances.

2. What you need to know before you take Rasitrio

Do not take Rasitrio
- if you are allergic to aliskiren, to amlodipine, to other dihydropyridine-derived medicines (known as calcium channel blockers), to hydrochlorothiazide, to sulphonamide-derived medicines (medicines used to treat chest or urinary infections) or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, do not take Rasitrio and ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren,
  - hereditary angioedema,
  - angioedema without any known cause.
- if you are more than 3 months pregnant. (It is also better to avoid Rasitrio in early pregnancy – see Pregnancy section).
- if you have serious liver problems.
- if you have serious kidney problems.
- if you have problems to produce urine (anuria).
- if the level of potassium in your blood is too low despite treatment.
- if the level of sodium in your blood is too low.
- if the level of calcium in your blood is too high.
- if you have gout (uric acid crystals in the joints).
- if you are taking any of the following medicines:
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis),
  - itraconazole (a medicine used to treat fungal infections),
  - quinidine (a medicine used to correct heart rhythm).
- if you have diabetes mellitus or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- if you have a very low blood pressure.
- if you are suffering from shock, including cardiogenic shock.
- if you have a narrowing of the aortic heart valve (aortic stenosis).
- if you have heart failure after an acute heart attack.

If any of the above applies to you, do not take Rasitrio and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Rasitrio:
- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce).
- if you have already experienced angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasitrio and contact your doctor.
- if you suffer from heart problems.
- if you are on a low-salt diet.
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis), including if you have had a kidney transplant or a narrowing or blockage of the arteries that supply blood to your kidney.
- if you have impaired kidney function, your doctor will carefully consider whether Rasitrio is suitable for you and may wish to monitor you carefully.
- if you suffer from liver problems (impaired liver function).
- if you have diabetes (high level of sugar in your blood).
- if you have a high level of cholesterol or triglycerides in your blood.
- if you suffer from a disease called lupus erythematosus (also called "lupus" or "SLE").

- if you suffer from allergy or asthma.
- if you are taking either of the following classes of medicines used to treat high blood pressure:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.
- if you are 65 years of age or older (see section Elderly (age 65 years or older) below).
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, restlessness, muscle pain or cramps, weakness, low blood pressure, reduced urine output, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide (contained in Rasitrio).
- if you experience skin reactions such as rash after sun exposure.
- if you experience a decrease in vision or eye pain. These could be symptoms of an increase of pressure in your eye and can happen within hours to weeks of taking Rasitrio. This can lead to permanent vision impairment, if not treated.
- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body.

You must tell your doctor if you think you are (or might become) pregnant. Rasitrio is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see Pregnancy section).

Children and adolescents
The use of Rasitrio in children and adolescents up to 18 years of age is not recommended.

Elderly
You should tell your doctor if you are 65 years of age or older because you may be more susceptible to side effects related to low blood pressure (see section 4 on possible side effects). Your doctor will carefully consider whether Rasitrio is suitable for you. If you are 75 years of age or older, your doctor may wish to monitor your blood pressure more frequently.

In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasitrio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Rasitrio and talk to your doctor if you are taking any of the following medicines:
- ciclosporin (a medicine used in transplantation to prevent organ rejection and also in other conditions, e.g. rheumatoid arthritis or atopic dermatitis).
- itraconazole (a medicine used to treat fungal infections).
- quinidine (a medicine used to correct heart rhythm).
- one of the following classes of medicines used to treat high blood pressure if you have diabetes mellitus or impaired kidney function:
  - an “angiotensin converting enzyme inhibitor” such as enalapril, lisinopril, ramipril etc.
  or
  - an “angiotensin II receptor blocker” such as valsartan, telmisartan, irbesartan etc.

Tell your doctor if you are using the following medicines:
- medicines or substances that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- medicines that may reduce the amount of potassium in your blood, such as diuretics (water tablets), corticosteroids, laxatives, carbenoxolone, amphotericin or penicillin G.
- medicines to reduce blood pressure, including methyldopa.
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- medicines that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- ketonazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections.
- amiodarone, a medicine used to treat abnormal heart rhythms.
- atorvastatin, a medicine used to treat high cholesterol.
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- rifampicin, a medicine used to prevent or treat infections.
- St. John's wort *(hypericum perforatum)*, a herbal medicine used to elevate mood.
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors) (used especially in the patients over 65 years old).
- diltiazem, a medicine used to treat heart problems.
- ritonavir, a medicine used to treat viral infection.
- lithium (a medicine used to treat some types of depression).
- some laxatives.
- medicines for the treatment of gout, such as allopurinol.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- one of the following classes of medicines used to treat high blood pressure:
  - an "angiotensin converting enzyme inhibitor" such as enalapril, lisinopril, ramipril etc.

  or
  - an "angiotensin II receptor blocker" such as valsartan, telmisartan, irbesartan etc.
- medicines used to control heart rhythm.
- medicines for the treatment of diabetes (oral agents such as metformin or insulins).
- medicines that may increase blood sugar level, such as beta blockers and diazoxide.
- steroids.
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- arthritis medicines.
- medicines used to treat oesophageal ulceration and inflammation (e.g. carbenoxolone).
- muscle relaxants (medicines to relax the muscles which are used during operations).
- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- anticholinergic agents (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling).
- some medicines used to treat infections, such as ketoconazole, amphotericin or penicillin G.

Rasitrio with food and drink
You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine with grapefruit juice.

Due to hydrochlorothiazide contained in Rasitrio, if you drink alcohol while on treatment with this medicine, you may have an increased feeling of dizziness on standing up, especially when getting up from a sitting position.

Pregnancy
Do not take this medicine if you are pregnant (see section Do not take Rasitrio). If you become pregnant while taking this medicine stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking Rasitrio before you become pregnant and will advise you to take another medicine instead of Rasitrio. Rasitrio is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasitrio is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
This medicine may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasitrio

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasitrio is one tablet a day.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should not take this medicine together with grapefruit juice.

If you take more Rasitrio than you should
If you have accidentally taken too many Rasitrio tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasitrio
If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. If it is almost time for your next dose you should simply take the next tablet at the usual time. **Do not** take a double dose (two tablets at once) to make up for a forgotten tablet.

Do not stop taking this medicine, even if you are feeling well (unless your doctor tells you to do so). People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects reported for Rasitrio are:
Common *(may affect up to 1 in 10 people)*
- dizziness
- low blood pressure
- swelling of hands, ankles and feet (peripheral oedema).

Tell your doctor immediately if you experience the following at the beginning of your treatment:
Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasitrio. Patients 65 years of age or older are more susceptible to side effects related to low blood pressure. In clinical trials low blood pressure occurred more frequently in patients taking Rasitrio than those taking only dual combinations of aliskiren/amlodipine, aliskiren/hydrochlorothiazide or amlodipine/hydrochlorothiazide (see section 2).

The following, possibly serious, side effects have been reported with medicines containing aliskiren, amlodipine or hydrochlorothiazide alone.

Aliskiren
Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder).

Possible side effects
Common *(may affect up to 1 in 10 people)*
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness.

Uncommon *(may affect up to 1 in 100 people)*
- skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below)
- kidney problems including acute renal failure (severely decreased urine output)
- swelling of hands, ankles or feet (peripheral oedema)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions – red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- low blood pressure
- palpitations
- cough
- itching, itchy rash (urticaria)
- increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*
- severe allergic reaction (anaphylactic reaction)
- allergic reactions (hypersensitivity)
- angioedema (the symptoms of which can include difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, hands and feet, eyes, lips and/or tongue, dizziness)
- increased level of creatinine in the blood
- red skin (erythema).

Amlodipine
In patients taking amlodipine alone, the following have been reported:
Common *(may affect up to 1 in 10 people)*
- sleepiness
- dizziness
- headache (especially at the beginning of treatment)
- hot flushes
- abdominal pain
- nausea
- ankle swelling
- swelling
- tiredness
- palpitations (awareness of your heart beat).

Uncommon *(may affect up to 1 in 100 people)*
- insomnia
- mood changes (including anxiety)
- depression
- trembling
- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- low blood pressure
- breathlessness
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration

- excessive sweating
- itching; rash
- generalised rash
- joint pain
- muscle pain
- muscle cramps
- back pain
- urination disorders
- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease.

Rare *(may affect up to 1 in 1,000 people)*
- confusion.

Very rare *(may affect up to 1 in 10,000 people)*
- low level of white blood cells and blood platelets
- allergic reaction with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- cough
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver
- liver disorder which can occur together with yellow skin and eyes, or dark-coloured urine
- abnormal liver function test
- angioedema (difficulties in breathing, or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue)
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth; dry skin, rash, itchy rash
- skin rash with flaking or peeling; rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun.

<u>Hydrochlorothiazide</u>
In patients taking hydrochlorothiazide alone, the following have been reported, however the frequency cannot be estimated from the available data:
Very common *(may affect more than 1 in 10 people)*
- low level of potassium in the blood
- increase of lipids in the blood.

Common *(may affect up to 1 in 10 people)*
- high level of uric acid in the blood
- low level of magnesium in the blood
- low level of sodium in the blood
- dizziness, fainting on standing up
- reduced appetite
- nausea and vomiting
- itchy rash and other types of rash
- inability to achieve or maintain erection.

Rare *(may affect up to 1 in 1,000 people)*
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)
- high level of calcium in the blood
- high level of sugar in the blood
- worsening of the diabetic metabolic state
- sad mood (depression)
- sleep disturbances
- dizziness
- headache
- tingling or numbness
- vision disorder
- irregular heart beat
- abdominal discomfort
- constipation
- diarrhoea
- liver disorders which can occur together with yellow skin and eyes
- increased sensitivity of skin to the sun
- sugar in the urine.

Very rare *(may affect up to 1 in 10,000 people)*
- fever, sore throat or mouth ulcers, more frequent infections (lack or low level of white blood cells)
- pale skin, tiredness, breathlessness, dark-coloured urine (haemolytic anaemia)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (hypersensitivity reactions)
- confusion, tiredness, muscle twitching and spasm, rapid breathing (hypochloraemic alkalosis)
- difficulty breathing with fever, coughing, wheezing, breathlessness (respiratory distress including pneumonitis and pulmonary oedema)
- severe upper stomach pain (pancreatitis)
- facial rash, joint pain, muscle disorder, fever (lupus erythematosus)
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever (vasculitis)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (toxic epidermal necrolysis).

Not known *(frequency cannot be estimated from the available data)*
- weakness
- bruising and frequent infections (aplastic anaemia)
- decrease in vision or pain in your eyes due to high pressure (possible signs of acute-angle closure glaucoma)
- severe skin disease that causes rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (erythema multiforme)
- muscle spasm
- severely decreased urine output (possible signs of renal disorder or renal failure), weakness (asthenia)
- fever.

If any of these affect you severely, tell your doctor. You may need to stop Rasitrio.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Rasitrio

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.
Do not store above 30°C.
Store Rasitrio tablets in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rasitrio contains
- Each Rasitrio 300 mg/10 mg/25 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate), 10 mg amlodipine (as besylate) and 25 mg hydrochlorothiazide. The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172).

What Rasitrio looks like and contents of the pack
- Rasitrio 300 mg/10 mg/25 mg film-coated tablets are brown, oval tablets, with "VIV" debossed on one side and "NVR" on the other.

Rasitrio is available in packs containing 14, 28, 56, 98 tablets in calendar blisters.
It is also available in multi-packs of 98 tablets (2 packs of 49) in calendar blisters.

Rasitrio is available in packs containing 30 or 90 tablets in blisters.
Rasitrio is available in packs containing 56x1 tablet in perforated unit dose blister.
It is also available in multi-packs of 98x1 tablet (2 packs of 49x1) in perforated unit dose blister.

Not all pack sizes may be available in your country.

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Other sources of information
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