ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
Rasilez HCT 150 mg/25 mg film-coated tablets
Rasilez HCT 300 mg/12.5 mg film-coated tablets
Rasilez HCT 300 mg/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rasilez HCT 150 mg/12.5 mg film-coated tablets
Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

Excipients with known effect:
Each tablet contains 25 mg lactose (as monohydrate) and 24.5 mg wheat starch.

Rasilez HCT 150 mg/25 mg film-coated tablets
Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients with known effect:
Each tablet contains 50 mg lactose (as monohydrate) and 49 mg wheat starch.

Rasilez HCT 300 mg/12.5 mg film-coated tablets
Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

Excipients with known effect:
Each tablet contains 25 mg lactose (as monohydrate) and 24.5 mg wheat starch.

Rasilez HCT 300 mg/25 mg film-coated tablets
Each film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

Excipients with known effect:
Each tablet contains 50 mg lactose (as monohydrate) and 49 mg wheat starch.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Rasilez HCT 150 mg/12.5 mg film-coated tablets
White, biconvex, ovaloid film-coated tablet imprinted with “LCI” on one side and “NVR” on the other.

Rasilez HCT 150 mg/25 mg film-coated tablets
Pale yellow, biconvex, ovaloid film-coated tablet imprinted with “CLL” on one side and “NVR” on the other.

Rasilez HCT 300 mg/12.5 mg film-coated tablets
Violet white, biconvex, ovaloid film-coated tablet imprinted with “CVI” on one side and “NVR” on the other.

Rasilez HCT 300 mg/25 mg film-coated tablets
Light yellow, biconvex, ovaloid film-coated tablet imprinted with “CVV” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone.

Rasilez HCT is indicated as substitution therapy in patients adequately controlled with aliskiren 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 Rasilez HCT is one tablet per day.

The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks.

Posology in patients not adequately controlled with aliskiren or hydrochlorothiazide monotherapy
Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Rasilez HCT 150 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 12.5 mg alone.
Rasilez HCT 150 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or hydrochlorothiazide 25 mg alone or by Rasilez HCT 150 mg/12.5 mg.
Rasilez HCT 300 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg or hydrochlorothiazide 12.5 mg alone or by Rasilez HCT 150 mg/12.5 mg.
Rasilez HCT 300 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg or hydrochlorothiazide 25 mg alone or by Rasilez HCT 300 mg/12.5 mg or Rasilez HCT 150 mg/25 mg.

If blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of Rasilez HCT 300 mg/25 mg daily. Dosing should be individualised and adjusted according to the patient's clinical response.

Posology as substitution therapy
For convenience, patients receiving aliskiren and hydrochlorothiazide from separate tablets may be switched to a fixed combination tablet of Rasilez HCT containing the same component doses.

Special populations
Renal impairment
Due to the hydrochlorothiazide component, Rasilez HCT is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2). No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
Rasilez HCT is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment or progressive liver disease. No

adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly people (over 65 years)
The recommended starting dose of aliskiren in elderly 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.

Paediatric population
The safety and efficacy of Rasilez HCT in children below 18 years have not yet been established. No data are available.

Rasilez HCT is contraindicated in children from birth to less than 2 years. Rasilez HCT should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3). The safety and efficacy of Rasilez HCT in children aged 6 to 17 years have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2. Use of Rasilez HCT is not recommended in this population.

Method of administration
Oral use. The tablets should be swallowed whole with some water. Rasilez HCT should be taken once a day, always with or always without food, preferably at the same time each day. Patients should establish a convenient daily schedule of medicinal product intake and maintain a steady temporal relationship with food intake. Concomitant intake with fruit juice and/or drinks containing plant extracts (including herbal teas) should be avoided (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to other sulfonamide-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 Rasilez HCT with an angiotensin converting enzyme inhibitors (ACEI) or an angiotensin II receptor blockers (ARB) is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Children from birth to less than 2 years (see sections 4.2 and 5.3).

4.4 Special warnings and precautions for use

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate

protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

General
In the event of severe and perisistent diarrhoea, Rasilez HCT therapy should be stopped (see section 4.8).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and decreased 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 RAAS by combining aliskiren with an ACEI or an ARB is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Heart failure
Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV) (see section 5.1). Rasilez HCT should be used with caution in patients with heart failure due to limited clinical efficacy and safety data.

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 Rasilez HCT 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 Rasilez HCT, or the treatment should start under close medical supervision.

Electrolyte imbalance
Treatment with Rasilez HCT 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 Rasilez HCT should be discontinued until stable correction of the potassium balance. Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with aliskiren may reduce diuretic-induced hypokalaemia. 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 (see sections 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 Rasilez HCT therapy, the treatment should be discontinued until normalisation of natraemia.

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

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. Rasilez HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasilez HCT 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 impairment and kidney transplantation
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Rasilez HCT is used in patients with renal impairment, periodic monitoring of serum electrolytes including potassium, creatinine and uric acid serum levels is recommended. Rasilez HCT is contraindicated in patients with severe renal impairment or anuria (see section 4.2 and 4.3)
There is no experience regarding the administration of Rasilez HCT in patients who have recently undergone kidney transplantation. Rasilez HCT should be used with caution in patients who have recently undergone kidney transplantation due to limited clinical efficacy and safety data.

Caution should be exercised when aliskiren 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. 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.

Hepatic impairment
There are no data with Rasilez HCT in patients with hepatic impairment. Rasilez HCT is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment or progressive liver disease. No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Renal artery stenosis and renovascular hypertension
No controlled clinical data are available on the use of Rasilez HCT in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, 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). 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 product 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).

In a post-authorisation observational study, the co-administration of aliskiren with ACEIs or ARBs has been associated with an increased risk of angioedema. The mechanism of this effect has not been established. In general, dual blockade of the RAAS by combining aliskiren with an ACEI or an ARB is not recommended (see section "Dual blockade of the renin-angiotensin-aldosterone system (RAAS)" above and also sections 4.5 and 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with a 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, Rasilez HCT 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.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus. In the event that any signs or clinical suspicion of systematic lupus erythematosus (SLE), Rasilez HCT should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred.

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 agents may be required.

Due to the hydrochlorothiazide component, Rasilez HCT 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. Rasilez HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Rasilez HCT 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.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Rasilez HCT, 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.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

General
Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

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

Excipients
Rasilez HCT contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Rasilez HCT contains wheat starch. Wheat starch in this medicine contains only very low levels of gluten (less than 100ppm) and is very unlikely to cause problems if you have coeliac disease. One dosage unit contains no more than 100 micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. You should consult your doctor prior to taking this medicine.

Paediatric population
Aliskiren is a P-glycoprotein (P-gp) substrate, and there is a potential for aliskiren overexposure in children with an immature P-gp drug transporter system. The age at which the transporter system is mature cannot be determined (see sections 5.2 and 5.3). Therefore, Rasilez HCT is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years (see section 4.2 and 4.3). The safety and efficacy of aliskiren in children aged 6 to 17 years have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2.

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasilez HCT interactions

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, adrenocorticotropic 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-administration with an agent affecting the level of serum potassium is considered necessary, caution is advisable (see sections 4.4 and 5.1).

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium is recommended when Rasilez HCT 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

NSAIDs may reduce the anti-hypertensive 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 Rasilez HCT with an NSAID requires caution, especially in elderly patients.

Other antihypertensive medicinal products
The antihypertensive effect of Rasilez HCT may be increased with the concomitant use of other antihypertensive agents. Therefore, caution should be used if coadmnistering with any other hypertensive agents

Additional information on aliskiren interactions

Contraindicated (see section 4.3)

P-gp potent inhibitors
A single dose 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)

Fruit juice and drinks containing plant extracts
Administration of fruit juice with aliskiren resulted in a decrease in AUC and C_{max} of aliskiren. Co-administration of grapefruit juice 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. Co-administration of orange or apple juice with aliskiren 150 mg resulted in a 62% decrease in aliskiren AUC or in a 63% decrease in aliskiren AUC, respectively. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by components of fruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, fruit juice should not be taken together with Rasilez HCT. The effect of drinks containing plant extracts (including herbal teas) on the absorption of aliskiren has not been investigated. However, compounds potentially inhibiting organic anion transporting polypeptide-mediated uptake of aliskiren are widely present in fruits, vegetables, and many other plant products. Therefore, drinks containing plant extracts, including herbal teas, should not be taken together with Rasilez HCT.

Dual blockade of the RAAS with aliskiren, ARBs or ACEIs
Clinical study data has shown that dual blockade of the RAAS through the combined use of ACEIs, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, stroke, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

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 (see section 5.2). 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 studies. 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-medication with an agent affecting the level of serum potassium is considered necessary, routine monitoring of potassium levels would be advisable.

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

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 section 'Organic anion transporting polypeptide (OATP' below) 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
Although meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially, the efficacy of aliskiren was shown to be similar when taken either with a light meal or

without a meal (see section 4.2). The available clinical data do not suggest an additive effect of different types of foods and/or drinks, however the potential for decreased aliskiren bioavailability due to this additive effect has not been studied and therefore cannot be excluded. Concomitant administration of aliskiren with fruit juice or drinks containing plant extracts, including herbal teas, should be avoided.

Pharmacokinetic interactions with other medicinal products
Compounds that have been investigated in 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 section "Fruit juice and drinks containing plant extracts" above).).

Additional information on hydrochlorothiazide interactions
When administered concurrently, the following medicinal products may interact with thiazide diuretics:

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.

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.

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.

Digoxine or other digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

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.

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.

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.

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.

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.

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

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 dose 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.

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

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

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.

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.

4.6 Fertility, pregnancy and lactation

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 RAAS have been associated with serious foetal malformations and neonatal death when used during second and third trimesters. 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.

No specific clinical studies have been performed with this combination, therefore Rasilez HCT should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. If pregnancy is detected during therapy, Rasilez HCT should be discontinued as soon as possible.

Breast-feeding
It is not known whether aliskiren is 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 Rasilez HCT during breast-feeding is not recommended. If Rasilez HCT is used during breast-feeding, doses should be kept as low as possible.

Fertility
There are no clinical data on fertility.

4.7 Effects on ability to drive and use machines

Rasilez HCT has minor influence on the ability to drive and use machines. When driving vehicles or using machines, it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasilez HCT.

4.8 Undesirable effects

Summary of the safety profile

The safety of Rasilez HCT has been evaluated in more than 3,900 patients, including over 700 treated for over 6 months, and 190 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Treatment with Rasilez HCT had an overall incidence of adverse experiences at doses up to 300 mg/25 mg similar to placebo. The most common adverse reaction observed with Rasilez HCT is diarrhoea. The adverse reactions previously reported with one of the individual components of Rasilez HCT (aliskiren and hydrochlorothiazide) and included in the tabulated list of adverse reactions may occur with Rasilez HCT.

Tabulated list of adverse reactions

The frequency of adverse reactions listed below is defined 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions observed with Rasilez HCT or with monotherapy with one or both of the two components are included in the table below. For adverse reactions observed with more than one component of a fixed-dose combination, the highest frequency is listed in the table below.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders	
Rare	Thrombocytopenia sometimes with purpura[h]
Very rare	Agranulocytosis[h], bone marrow depression[h], haemolytic anaemia[h], leucopenia[h]
Not known	Aplastic anaemia[h]
Immune system disorders	
Rare	Anaphylactic reactions[a], hypersensitivity reactions[a,h]
Metabolism and nutrition disorders	
Very common	Hypokalaemia[h]
Common	Hyperuricaemia[h], hypomagnesaemia[h]
Rare	Hypercalcaemia[h], hyperglycaemia[h], worsening of diabetic metabolic state[h]
Very rare	Hypochloraemic alkalosis[h]
Psychiatric disorders	
Rare	Depression[h], sleep disturbances[h]
Nervous system disorders	
Rare	Headache[h], paraesthesia[h]
Eye disorders	
Rare	Visual impairment[h]
Not known	Acute angle-closure glaucoma[h], choroidal effusion[h]
Ear and labyrinth disorders	
Not known	Vertigo[a]
Cardiac disorders	
Common	Dizziness[a,h]
Uncommon	Palpitations[a], oedema peripheral[a]
Rare	Cardiac arrhythmias[h]

Vascular disorders	
Common	Orthostatic hypotension[h]
Uncommon	Hypotension[c,a]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough[a]
Very rare	Respiratory distress (including pneumonitis and pulmonary oedema) [h]
Not known	Dyspnoea[a]
Gastrointestinal disorders	
Common	Diarrhoea[c,a,h], decreased appetite[h], nausea and vomiting[a,h]
Rare	Abdominal discomfort[h], constipation[h]
Very rare	Pancreatitis[h]
Hepatobiliary disorders	
Rare	Intrahepatic cholestasis[h], jaundice[a,h]
Not known	Liver disorder[a,]*, hepatitis[a], liver failure[a,]**
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash[a,h]
Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome[a], toxic epidermal necrolysis (TEN)[a], oral mucosal reactions[a], pruritus[a]
Rare	Angioedema[a], erythema[a], photosensitivity reactions[h]
Very rare	Cutaneous lupus erythematosus-like reactions[h], reactivation of cutaneous lupus erythematosus[h], vasculitis necrotising and toxic epidermal necrolysis[h]
Not known	Erythema multiforme[h]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia[a]
Not known	Muscle spasm[h]
Renal and urinary disorders	
Uncommon	Acute renal failure[a,h], renal impairment[a]
Not known	Renal dysfunction[h]
Reproductive system and breast disorders	
Common	Impotence[h]
General disorders and administration site conditions	
Not known	Asthenia[h], pyrexia[h]
Investigations	
Very common	Increases in cholesterol and triglycerides[h]
Common	Hyperkalaemia[a], hyponatraemia [c, a, h]
Uncommon	Liver enzyme increased[a]
Rare	Haemoglobin decreased[a], haematocrit decreased[a], blood creatinine increased[a], glycosuria[h]

[c] Adverse reaction observed with Rasilez HCT
[a] Adverse reaction observed with monotherapy with aliskiren
[h] Adverse reaction observed with monotherapy with hydrochlorothiazide
* 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 reactions

Diarrhoea
Diarrhoea is a dose-related adverse reaction for aliskiren. In controlled clinical study, the incidence of diarrhoea in Rasilez HCT-treated patients was 1.3% compared to 1.4% for aliskiren- or 1.9% for hydrochlorothiazide-treated patients.

Serum potassium
In a large placebo-controlled clinical study, the opposite effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 25 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum potassium to detect possible electrolyte imbalance should be performed in patients at risk at appropriate intervals (see sections 4.4 and 4.5).

Additional information on individual components

Adverse reactions previously reported with one of the individual components may occur with Rasilez HCT even if not observed in clinical study.

Aliskiren
Hypersensitivity reactions including anaphylactic reactions and angioedema have occurred during treatment with aliskiren.

In controlled clinical study, 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).

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 agents acting on the renin-angiotensin system, 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.

Paediatric population

Aliskiren has been evaluated for safety in a randomised, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years, mostly overweight/obese, followed by an extension

study including 208 patients treated for 52 weeks. An additional 52 to 104 weeks non-interventional observational extension study in 106 patients (no study treatment administered) was conducted with the objective to evaluate the long-term safety in terms of growth and development of children 6-17 years of age with hypertension (primary or secondary) at baseline in the core study, previously treated with aliskiren.
The frequency, type and severity of adverse reactions in children were generally similar to those seen in hypertensive adults. No overall clinically relevant adverse impact in paediatric patients aged 6 to 17 years was observed after treatment with aliskiren for up to one year based on physical development, assessed in patients with primary or secondary hypertension, and neurocognitive development assessed only in patients with secondary hypertension (19 patients: 9 previously treated with aliskiren and 10 previously treated with enalapril). See section 4.2, 4.8, 5.1 and 5.2 for information on paediatric use.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasilez HCT. The adverse reactions listed in the table above, which are marked with the reference "h", have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

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, supportive treatment should be initiated.

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 inhibitor, ATC code: C09XA52

Rasilez HCT combines two antihypertensive active substances to control blood pressure in patients with essential hypertension: Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

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 agents that inhibit the RAAS (angiotensin converting enzyme inhibitors (ACEI) and angiotension 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 agents. The clinical implications of the effects on PRA are not known at the present time.

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 (12 months), and was independent of age, gender, body mass index and ethnicity.

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 efficacious and well tolerated.

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 doses 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 a 8-week study in 754 hypertensive elderly (≥ 65 years) and very elderly patients (30% ≥ 75 years) 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. In a pooled analysis of efficacy and safety data from clinical study up to 12 months duration, there was no statistically significant difference in blood pressure reduction between aliskiren 300 mg and aliskiren 150 mg in elderly patients (≥ 65 years).

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. 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. The final study results indicated a hazard ratio for the primary endpoint of 1.097 in favour of placebo (95.4% Confidence Interval: 0.987, 1.218, 2-sided p=0.0787). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (38.2% versus 30.3%). In particular there was an increased incidence of renal dysfunction (14.5% versus 12.4%), hyperkalaemia (39.1% versus 29.0%), hypotension-related events (19.9% versus 16.3%) and adjudicated stroke endpoints (3.4% versus 2.7%). The increased incidence of stroke was greater in patients with renal insufficiency.

Aliskiren 150 mg (increased to 300 mg if tolerated) added to conventional therapy was evaluated in a double-blind placebo-controlled randomised trial in 1,639 patients with reduced ejection fraction hospitalised for an episode of acute heart failure (NYHA Class III–IV) who were haemodynamically stable at baseline. The primary endpoint was cardiovascular death or heart failure rehospitalisation within 6 months; secondary endpoints were assessed within 12 months.

The study showed no benefit of aliskiren when administered on top of standard therapy for acute heart failure and an increased risk of cardiovascular events in patients with diabetes mellitus. Study results indicated a non-significant effect of aliskiren with a hazard ratio of 0.92 (95% Confidence Interval: 0.76-1.12; p=0.41, aliskiren vs. placebo). Different treatment effects of aliskiren were reported for overall mortality within 12 months dependent on diabetes mellitus status. In the subgroup of patients with diabetes mellitus the hazard ratio was 1.64 in favour of placebo (95% Confidence Interval: 1.15-2.33), whereas the hazard ratio in the subgroup of patients without diabetes was 0.69 in favour of aliskiren (95% Confidence Interval: 0.50-0.94); p-value for interaction = 0.0003. An increased incidence of hyperkalaemia (20.9% versus 17.5%), renal impairment/renal failure (16.6% versus 12.1%) and hypotension (17.1% versus 12.6%) was observed in the aliskiren group compared with placebo and was greater in patients with diabetes.

Aliskiren was evaluated for cardiovascular mortality and morbidity benefit in a double-blind active controlled randomised study in 7,064 patients with chronic heart failure and reduced left ventricular ejection fraction, of which 62% had a history of hypertension. The primary endpoint was a composite of cardiovascular death and first hospitalisation for heart failure.

In this study, aliskiren at a target dose of 300 mg was compared to enalapril at a target dose of 20 mg when added to standard of care which included a beta blocker (and a mineralocorticoid receptor antagonist in 37% of patients) and a diuretic as needed. The study also evaluated the combination of aliskiren and enalapril. Mean duration of follow-up was 3.5 years. The final results of the study did not demonstrate statistically that aliskiren was non-inferior to enalapril on the primary endpoint, however there was essentially no difference in the observed incidence rates between aliskiren and enalapril (hazard ratio of 0.99 with 95% Confidence Interval: 0.90-1.10). There was no significant benefit of adding aliskiren to enalapril (primary endpoint: hazard ratio of 0.93 with 95% Confidence Interval: 0.85-1.03; p=0.1724, combination versus enalapril). Treatment effects were similar in patients with

diabetes and with renal insufficiency. The incidence of adjudicated stroke was not significantly different between the aliskiren and enalapril groups (4.4% versus 4.0%; HR 1.12, 95% CI 0.848, 1.485) or between the combination and enalapril groups (3.7% versus 4.0%; HR 0.93, 95% CI 0.697, 1.251). The incidence of adverse events tended to be higher in patients with diabetes, or with GFR <60 ml/min/1.73 m², or with age ≥ 65 years; however, there was no difference between patients treated with aliskiren and those treated with enalapril.

The incidence of certain adverse events was similar between aliskiren and enalapril groups while there was an increased incidence of adverse events with the combination of aliskiren and enalapril: hyperkalaemia (21.4%, 13.2%, and 15.9% for combination, aliskiren and enalapril respectively); renal impairment/renal failure (23.2%, 17.4% and 18.7%) and hypotension related events (27.0%, 22.3% and 22.4%).

There was a statistically significant increased incidence of syncope with the combination of aliskiren and enalapril compared to enalapril in the overall population (4.2% versus 2.8%; RR 1.51, 95% CI 1.11-2.05) and in the subgroups NYHA I/II overall (4.8% versus 3.0%; RR 1.62, 95% CI 1.14-2.29).

The incidence of atrial fibrillation was 11.1%, 13.3%, and 11.0% in the combination, aliskiren, and enalapril groups, respectively.

Statistically significantly higher incidences in the occurrence of cardiac failure and ischaemic stroke were also found for aliskiren compared to enalapril in patients with NYHA I/II with hypertension, and in the occurrence of chronic cardiac failure and ventricular extrasystole in patients with NYHA III/IV with hypertension. For the combination of aliskiren and enalapril there were statistically significant differences in the rate of angina unstable compared to enalapril.

No clinically relevant differences in efficacy or safety results were observed in the subpopulation of elderly patients with a history of hypertension and chronic heart failure Class I-II compared to the overall study population.

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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Aliskiren/hydrochlorothiazide

Over 3,900 hypertensive patients received Rasilez HCT once daily in clinical study.

In hypertensive patients, once-daily administration of Rasilez HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within 1 week and the maximum effect is generally seen within 4 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of the aliskiren treatment (aliskiren with or without hydrochlorothiazide add-on), the return of blood pressure towards baseline was gradual (3-4 weeks) with no evidence of the rebound effect.

Rasilez HCT was studied in a placebo-controlled trial including 2,762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Rasilez HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared to 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly greater than the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralised the reactive increase of PRA caused by hydrochlorothiazide.

When administered in hypertensive patients with markedly elevated blood pressure (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg), Rasilez HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg administered without up-titration from monotherapy demonstrated significantly greater systolic/diastolic blood pressure control rates (< 140/90 mmHg) as compared to the respective monotherapies. In this population, Rasilez HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which were significantly superior to the respective monotherapies. The safety of the combination therapy was similar to the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse events were uncommon with the combination treatment, with no increased incidence in elderly patients.

In a study in 880 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than aliskiren 300 mg monotherapy. In a study in 722 randomised patients not adequately responsive to hydrochlorothiazide 25 mg treatment, the combination of aliskiren/hydrochlorothiazide 300 mg/25 mg produced systolic/diastolic blood pressure reductions of 16.78/10.7 mmHg, which were significantly greater than hydrochlorothiazide 25 mg monotherapy.

In another clinical studies, the efficacy and safety of Rasilez HCT were also assessed in 489 obese hypertensive patients who did not respond to hydrochlorothiazide 25 mg (baseline systolic/diastolic blood pressure 149.4/96.8 mmHg). In this difficult-to-treat population, Rasilez HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg compared to 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with similar safety to hydrochlorothiazide monotherapy.

In a study in 183 randomised patients with severe hypertension (mean sitting diastolic blood pressure ≥ 105 and < 120 mmHg), aliskiren treatment regimen with optional addition of hydrochlorothiazide 25 mg was shown to be safe and efficacious in reducing blood pressure.

Paediatric population

In a multicentre, randomised, double-blind, 8-week study with aliskiren monotherapy (3 dose groups by weight category [≥20 kg to <50 kg; ≥50 kg to <80 kg; ≥80 kg to ≤150 kg]: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, mostly overweight/obese, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dose-finding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mid, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were <0.2 mmHg. The treatment with aliskiren was well tolerated in this study.

This study was extended with a 52-week double-blind, randomised study to evaluate the safety, tolerability and efficacy of aliskiren compared to enalapril in 208 paediatric hypertensive patients aged 6 to 17 years (at baseline in the previous study). The starting dose in each group was assigned depending on weight with three groups: ≥20 to <50 kg, ≥50 to <80 kg, and ≥80 to ≤150 kg. The starting doses for aliskiren were 37.5/75/150 mg in the low, mid and high weight groups, respectively. The starting doses for enalapril were 2.5/5/10 mg in the low, mid and high weight groups, respectively. Optional titration of the respective study drug doses to the next highest weight-based dose level was available by doubling the dose with each of the two allowed dose titrations, up to 600 mg (highest studied dose in adults) for aliskiren and 40 mg for enalapril in the ≥80 to ≤150 kg weight group, if medically necessary to control the mean sitting systolic blood pressure (i.e. msSBP should be less than the 90th percentile for age, gender and height). Overall, the mean age of the patients was 11.8 years with 48.6% of patients being in the 6-11 years age group and 51.4% in the 12-17 years age group. Mean weight was 68.0 kg with 57.7% of patients having BMI greater than or equal to the 95th percentile for age and gender. At the end of this extension study, changes in msSBP from baseline were similar with aliskiren compared to enalapril (-7.63 mmHg vs. -7.94 mmHg) in the full analysis set. However, the significance of the non-inferiority testing was not maintained when the analysis was performed on the per-protocol set in which the least square mean change in msSBP from baseline was -7.84 mmHg with aliskiren and -9.04 mmHg with enalapril. In addition, due to the possibility of up-titration if medically necessary to control the msSBP, no conclusion can be drawn on the appropriate posology of aliskiren in patients aged 6 to 17 years.

After the first 52 week extension study, eligible male and female paediatric patients aged 6 to 17 years with primary or secondary hypertension, were enrolled in a 52 to 104 week off-therapy non-interventional observational extension study designed to evaluate the LT growth and development, through height and weight measurement, with added neurocognitive and renal function evaluations as follow-up measures performed only in patients with secondary hypertension (19 patients: 9 previously treated with aliskiren and 10 previously treated with enalapril).

There were no statistically significant differences in the mean changes in weight, height, or BMI between the treatment groups from Baseline to LT Visit 18 (Week 104) (primary analysis).

In patients after 104 weeks (at LT Visit 19 [Week 156]), there were LS mean decreases from Baseline in weight and BMI in both treatment groups, with a slightly larger decrease in the aliskiren compared to the enalapril treatment group.

There was a greater LS mean increase from Baseline in height after 104 weeks (at LT Visit 19 [Week 156], secondary hypertension patients) compared to the increase observed after 52 weeks (at LT Visit 18 [Week 104], primary hypertension patients), which is expected in these growing paediatric patients.

Results of the neurocognitive assessments showed some improvements in most of the test scores, with no meaningful difference between the treatment groups.

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

5.2 Pharmacokinetic properties

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. However the efficacy of aliskiren was similar when taken with a light meal or under fasted state. 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.

Transporters
MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in pre-clinical studies.

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 (oral radioactive dose recovery = 91%). 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, the mean plasma clearance is approximately 9 l/h.

Linearity
Exposure to aliskiren increased slightly 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. Mechanisms responsible for the deviation from dose proportionality 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 to 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 results of this study did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

In an 8-week randomised, double-blind study with aliskiren monotherapy in 267 paediatric hypertensive patients aged 6 to 17 years, mostly overweight/obese, fasting trough aliskiren concentrations at day 28 were comparable to those observed in other studies in both adults and children using similar aliskiren doses.

Results from an in vitro MDR1 human tissue study suggested an age and tissue dependent pattern of MDR1 (P-gp) transporter maturation. A high inter-individual variability of mRNA expression levels was observed (up to 600-fold). Hepatic MDR1 mRNA expression was statistically significantly lower in samples from foetuses, neonates and infants up to 23 months.

The age at which the transporter system is mature cannot be determined. There is a potential for aliskiren overexposure in children with an immature MDR1 (P-gp) system (see section "Transporters" above and sections 4.2, 4.4 and 5.3).

Hydrochlorothiazide

Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). The increase in mean AUC is linear and dose proportional in the therapeutic range.

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.

Aliskiren/hydrochlorothiazide
Following oral administration of Rasilez HCT tablets, the median peak plasma concentration time is within 1 hour for aliskiren and 2.5 hours for hydrochlorothiazide.

The rate and extent of absorption of Rasilez HCT are equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. Similar food effect was observed for Rasilez HCT as for the individual monotherapies.

Characteristics in patients

Rasilez HCT has been shown to be effective as a once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

The pharmacokinetics of aliskiren are not significantly affected in patients with mild to moderate liver disease. Consequently, no initial dose adjustment of Rasilez HCT is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment treated by Rasilez HCT. Rasilez HCT is contraindicated in patients with severe hepatic impairment (see section 4.3).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.2 and 4.4). 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.

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).

No initial dose adjustment of Rasilez HCT is required in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

No pharmacokinetic data on Rasilez HCT are available in the paediatric population.

5.3 Preclinical safety data

Safety pharmacology studies with aliskiren 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 (gastrointestinal tract) irritation potential or the expected pharmacological effects of aliskiren.

No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant.

Although aliskiren has known local (gastrointestinal tract) 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.

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).

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.

The findings observed in the 2-week and 13-week toxicity studies were consistent with those observed previously with aliskiren or hydrochlorothiazide monotherapies. There were no new or unexpected findings observed of relevance to human use. Increased cellular vacuolation of the adrenal gland zona glomerulosa was observed during the 13-week toxicity study in rats. The finding was observed in animals treated with hydrochlorothiazide but not in those animals receiving aliskiren alone or vehicle. There was no evidence that this finding was enhanced in the aliskiren/hydrochlorothiazide combination as it was only apparent at a minimal severity in all animals.

Juvenile animal studies

In a juvenile toxicity study in 8-day-old rats, aliskiren administration at 100 mg/kg/day and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose) was associated with high mortality and severe morbidity. In another juvenile toxicity study in 14-day old rats, aliskiren administration at 300 mg/kg/day (8.5-fold the maximum recommended human dose) was associated with delayed mortality. The systemic exposure to aliskiren in 8-day old rats was >400-fold higher than in adult rats. Results from a mechanistic study showed that the MDR1 (P-gp) gene expression in juvenile rats was significantly lower when compared to adult rats. The increased aliskiren exposure in juvenile rats appears to be attributed mainly to lack of maturation of P-gp in the gastrointestinal tract. There is therefore a potential for aliskiren overexposure in paediatric patients with immature MDR1 efflux system (see sections 4.2, 4.3 and 5.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rasilez HCT 150 mg/12.5 mg film-coated tablets
Tablet core:
Microcrystalline cellulose
Crospovidone, type A
Lactose monohydrate
Wheat starch
Povidone, K-30
Magnesium stearate
Colloidal anhydrous silica
Talc

Coating:
Talc
Hypromellose substitution type 2910 (3 mPa·s)
Macrogol 4000
Titanium dioxide (E171)

Rasilez HCT 150 mg/25 mg film-coated tablets
Tablet core:
Microcrystalline cellulose
Crospovidone, type A
Lactose monohydrate
Wheat starch
Povidone, K-30
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose substitution type 2910 (3 mPa·s)
Macrogol 4000
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

Rasilez HCT 300 mg/12.5 mg film-coated tablets
Tablet core:
Microcrystalline cellulose
Crospovidone, type A
Lactose monohydrate
Wheat starch
Povidone, K-30
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose substitution type 2910 (3 mPa·s)
Macrogol 4000
Titanium dioxide (E171)
Red iron oxide (E172)
Black iron oxide (E172)

Rasilez HCT 300 mg/25 mg film-coated tablets
Tablet core:
Microcrystalline cellulose
Crospovidone, type A
Lactose monohydrate
Wheat starch
Povidone, K-30
Magnesium stearate
Silica colloidal anhydrous
Talc

Coating:
Talc
Hypromellose substitution type 2910 (3 mPa·s)
Macrogol 4000
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PA/Alu/PVC – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90 (3 packs of 30), 98 (2 packs of 49) or 280 (20 packs of 14) tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 (20 packs of 14) tablets.
Multi-packs (perforated unit dose blister) containing 98 (2 packs of 49 x 1) tablets.

Not all pack sizes or strengths 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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Rasilez HCT 150 mg/12.5 mg film-coated tablets
EU/1/08/491/001-020

Rasilez HCT 150 mg/25 mg film-coated tablets
EU/1/08/491/021-040

Rasilez HCT 300 mg/12.5 mg film-coated tablets
EU/1/08/491/041-060

Rasilez HCT 300 mg/25 mg film-coated tablets
EU/1/08/491/061-080

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 27 August 2018

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

Novartis Farma S.p.A.
Via Provinciale Schito 131
IT-80058 Torre Annunziata/NA
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
90 film-coated tablets
98 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/010	7 film-coated tablets
EU/1/08/491/011	14 film-coated tablets
EU/1/08/491/012	28 film-coated tablets
EU/1/08/491/013	30 film-coated tablets
EU/1/08/491/014	50 film-coated tablets
EU/1/08/491/015	56 film-coated tablets
EU/1/08/491/016	56 x 1 film-coated tablet
EU/1/08/491/017	90 film-coated tablets
EU/1/08/491/018	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/001	7 film-coated tablets
EU/1/08/491/002	14 film-coated tablets
EU/1/08/491/003	28 film-coated tablets
EU/1/08/491/004	30 film-coated tablets
EU/1/08/491/005	50 film-coated tablets
EU/1/08/491/006	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Noden Pharma DAC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets. Component of a multipack, can't be sold separately.
49 x 1 film-coated tablet. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/020	280 film-coated tablets (20 packs of14)
EU/1/08/491/019	98 film-coated tablets (2 packs of 49x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be sold separately.
90 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/009	280 film-coated tablets (20 packs of 14)
EU/1/08/491/007	90 film-coated tablets (3 packs of 30)
EU/1/08/491/008	98 film-coated tablets (2 packs of 49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49 x 1) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/019	98 film-coated tablets (2 packs of 49 x 1)
EU/1/08/491/020	280 film-coated tablets (20 packs of 14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 90 (3 packs of 30) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/008	98 film-coated tablets (2 packs of 49)
EU/1/08/491/009	280 film-coated tablets (20 packs of 14)
EU/1/08/491/007	90 film-coated tablets (3 packs of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
90 film-coated tablets
98 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/030	7 film-coated tablets
EU/1/08/491/031	14 film-coated tablets
EU/1/08/491/032	28 film-coated tablets
EU/1/08/491/033	30 film-coated tablets
EU/1/08/491/034	50 film-coated tablets
EU/1/08/491/035	56 film-coated tablets
EU/1/08/491/036	56 x 1 film-coated tablets
EU/1/08/491/037	90 film-coated tablets
EU/1/08/491/038	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/021	7 film-coated tablets
EU/1/08/491/022	14 film-coated tablets
EU/1/08/491/023	28 film-coated tablets
EU/1/08/491/024	30 film-coated tablets
EU/1/08/491/025	50 film-coated tablets
EU/1/08/491/026	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Noden Pharma DAC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/040	280 (20 x 14) film-coated tablets
EU/1/08/491/039	98 (2 x 49 x 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be sold separately.90 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/029	280 film-coated tablets (20 packs of 1)
EU/1/08/491/027	90 film-coated tablets (3 packs of 30)
EU/1/08/491/028	98 film-coated tablets (2 packs of 49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49 x 1) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/039	98 film-coated tablets (2 packs of 49x1)
EU/1/08/491/040	280 film-coated tablets (20 packs of 14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 150 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 90 (3 packs of 30) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/028	98 film-coated tablets (2 packs of 49)
EU/1/08/491/029	280 film-coated tablets (20 packs of 14)
EU/1/08/491/027	90 film-coated tablets (3 packs of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 150 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
90 film-coated tablets
98 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/050	7 film-coated tablets
EU/1/08/491/051	14 film-coated tablets
EU/1/08/491/052	28 film-coated tablets
EU/1/08/491/053	30 film-coated tablets
EU/1/08/491/054	50 film-coated tablets
EU/1/08/491/055	56 film-coated tablets
EU/1/08/491/056	56 x 1 film-coated tablet
EU/1/08/491/057	90 film-coated tablets
EU/1/08/491/058	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/041	7 film-coated tablets
EU/1/08/491/042	14 film-coated tablets
EU/1/08/491/043	28 film-coated tablets
EU/1/08/491/044	30 film-coated tablets
EU/1/08/491/045	50 film-coated tablets
EU/1/08/491/046	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Noden Pharma DAC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/060	280 film-coated tablets (20 packs of 14)
EU/1/08/491/059	98 film-coated tablets (2 packs of 49 x 1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack. Not to be sold separately.
90 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/049	280 film-coated tablets (20 packs of 14)
EU/1/08/491/047	90 film-coated tablets (3 packs of 30)
EU/1/08/491/048	98 film-coated tablets (2 packs of 49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49 x 1) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/059	98 film-coated tablets (2 packs of 49 x 1)
EU/1/08/491/060	280 film-coated tablets (20 packs of 14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/12.5 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 90 (3 packs of 30) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/048	98 film-coated tablets (2 packs of 49)
EU/1/08/491/049	280 film-coated tablets (20 packs of 14)
EU/1/08/491/047	90 film-coated tablets (3 packs of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
90 film-coated tablets
98 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/070	7 film-coated tablets
EU/1/08/491/071	14 film-coated tablets
EU/1/08/491/072	28 film-coated tablets
EU/1/08/491/073	30 film-coated tablets
EU/1/08/491/074	50 film-coated tablets
EU/1/08/491/075	56 film-coated tablets
EU/1/08/491/076	56 x 1 film-coated tablet
EU/1/08/491/077	90 film-coated tablets
EU/1/08/491/078	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/061	7 film-coated tablets
EU/1/08/491/062	14 film-coated tablets
EU/1/08/491/063	28 film-coated tablets
EU/1/08/491/064	30 film-coated tablets
EU/1/08/491/065	50 film-coated tablets
EU/1/08/491/066	56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/ALU/PVC)
BLISTER (CALENDAR) (PVC/PCTFE OR PA/ALU/PVC)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Noden Pharma DAC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/080	280 film-coated tablets (20 packs of 14)
EU/1/08/491/079	98 film-coated tablets (2 packs of 49 x 1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

280 film-coated tablets. Component of a multipack, can't be sold separately.
90 film-coated tablets. Component of a multipack, can't be sold separately.
98 film-coated tablets. Component of a multipack, can't 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/069	280 film-coated tablets (20 packs of 14)
EU/1/08/491/067	90 film-coated tablets (3 packs of 30)
EU/1/08/491/068	98 film-coated tablets (2 packs of 49)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PVC/PCTFE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
Aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49 x 1) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/079	98 film-coated tablets (2 packs 49 x 1)
EU/1/08/491/080	280 film-coated tablets (20 packs of 14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PA/ALU/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez HCT 300 mg/25 mg film-coated tablets
aliskiren/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose and wheat starch.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 98 (2 packs of 49) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 90 (3 packs of 30) film-coated 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 25°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

Noden Pharma DAC
D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/491/068	98 film-coated tablets (2 packs of 49)
EU/1/08/491/069	280 film-coated tablets (20 packs of 14)
EU/1/08/491/067	90 film-coated tablets (3 packs of 30)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez HCT 300 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Rasilez HCT 150 mg/12.5 mg film-coated tablets
Rasilez HCT 150 mg/25 mg film-coated tablets
Rasilez HCT 300 mg/12.5 mg film-coated tablets
Rasilez HCT 300 mg/25 mg film-coated tablets
Aliskiren/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. See section 4.

What is in this leaflet

1. What Rasilez HCT is and what is it used for

What Rasilez HCT is
This medicine contains two active substances, called aliskiren and hydrochlorothiazide. Both of these active substances help to control high blood pressure (hypertension).

Aliskiren is a renin inhibitor. It reduces the amount of angiotensin II the body can make. Angiotensin II causes blood vessels to tighten, which makes blood pressure higher. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.

Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics. Hydrochlorothiazide increases urine output, which also lowers blood pressure.

This helps to lower high blood pressure in adult patients. 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 Rasilez HCT is used for
This medicine is used to treat high blood pressure in adult patients. It is used in patients whose blood pressure is not adequately controlled by aliskiren or hydrochlorothiazide taken alone. It can also be used in patients whose blood pressure is adequately controlled with aliskiren and hydrochlorothiazide taken as separate tablets, to replace the same doses of the two active substances.

2. What you need to know before you take Rasilez HCT

Do not take Rasilez HCT
- if you are allergic to aliskiren or hydrochlorothiazide, to sulfonamide-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 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 this medicine in early pregnancy – see section 'Pregnancy'.
- if you have serious liver or serious kidney problems.
- if you are unable 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 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) or quinidine (a medicine used to correct heart rhythm).
- if you have diabetes 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
  or
  - an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan.
- if the patient is less than 2 years of age.

If any of the above applies to you, do not take Rasilez HCT and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Rasilez HCT:
- if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Rasilez HCT.
- if you have impaired kidney function, your doctor will carefully consider whether this medicine is suitable for you and may wish to monitor you carefully.
- if you have had a kidney transplant.
- if you suffer from liver problems.
- if you suffer from heart problems.
- 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 this medicine and contact your doctor.
- 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
  or
  - an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan.
- if you are on a low-salt diet.
- if you have signs and symptoms such as abnormal thirst, dry mouth, general weakness, drowsiness, muscle pain or cramps, nausea, vomiting, or an abnormally fast heart beat which may indicate an excessive effect of hydrochlorothiazide.
- 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 fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to a week of taking Rasilez HCT. This can lead to

permanent vision loss, if not treated. If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this.
- 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).

Your doctor may check your kidney function, blood pressure and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also section "Do not take Rasilez HCT".

You must tell your doctor if you think you are (or might become) pregnant. Rasilez HCT 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 section "Pregnancy").

Children and adolescents
This medicine must not be used in babies from birth to less than 2 years of age. It should not be used in children from 2 to less than 6 years of age, and is not recommended for use in children and adolescents from 6 to less than 18 years of age. This is because the safety and benefits of this medicine are not known in this population.

Elderly people
The usual recommended starting dose of aliskiren in elderly patients aged 65 years or older is 150 mg. 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 Rasilez HCT
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important to tell your doctor if you are using the following medicines:
- lithium (a medicine used to treat some types of depression).
- 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 that may induce "*torsades de pointes*" (irregular heart beat), such as antiarrhythmics (medicines used to treat heart problems) and some antipsychotics.
- medicines that may reduce the amount of sodium in your blood, such as antidepressants, antipsychotics, antiepileptics (carbamazepine).
- pain killers such as non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 inhibitors (Cox-2 inhibitors).
- medicines to reduce blood pressure, including methyldopa, an angiotensin II receptor blocker or an angiotensin converting enzyme inhibitor (see sections "Do not take Rasilez HCT" and "Warnings and precautions").
- medicines to increase blood pressure, such as noradrenaline or adrenaline.
- digoxin or other digitalis glycosides (medicines used to treat heart problems).
- vitamin D and calcium salts.
- 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.
- medicines for the treatment of gout, such as allopurinol.
- 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).

- amantadine (a medicine used to treat Parkinson's disease, also used to treat or prevent certain illnesses caused by viruses).
- cholestyramine, colestipol or other resins (substances used mainly to treat high levels of lipids in the blood).
- cytotoxic medicines (used to treat cancer), such as methotrexate or cyclophosphamide.
- muscle relaxants (medicines to relax the muscles which are used during operations).
- alcohol, sleeping pills and anaesthetics (medicines allowing patients to undergo surgery and other procedures).
- iodine contrast media (agents used for imaging examinations).
- arthritis medicines.

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, or water tablets, which are used to increase the amount of urine you produce.
- some medicines used to treat infections, such as ketoconazole.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat angina pectoris.

Rasilez HCT with food and drink
You should take this medicine either with a light meal or without a meal, once a day, preferably at the same time each day. You should avoid taking this medicine together with fruit juice and/or drinks containing plant extracts (including herbal teas), as it could cause a decrease in the effectiveness of this medicine

Pregnancy
Do not take this medicine if you are pregnant (see section 'Do not take Rasilez HCT'). 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 this medicine before you become pregnant and will advise you to take another medicine instead of this medicine. It is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. This medicine 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. If you experience this symptom, do not drive or use tools or machines.

Rasilez HCT contains lactose and wheat starch (containing gluten)
This medicine contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicinecontains wheat starch. Wheat starch in this medicine contains only very low levels of gluten and is very unlikely to cause problems if you have coeliac disease. One dosage unit contains no more than 100 micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. You should consult your doctor prior to taking this medicine.

3. How to take Rasilez HCT

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Rasilez HCT may have been prescribed to you because your previous treatment with a medicine containing one of the active components of Rasilez HCT did not lower your blood pressure enough. If this is the case, your doctor will tell you how to switch from that treatment to Rasilez HCT.

The usual dose of Rasilez HCT is one tablet a day. The blood pressure lowering effect is present within one week after beginning treatment.

Elderly people
The usual recommended starting dose of aliskiren in elderly patients is 150 mg. 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.

Method of administration
Swallow the tablet whole with some water. You should take this medicine once a day, always with or always without food, preferably at the same time each day. You should establish a convenient daily schedule to take the medicine the same way each day, in a regular pattern with respect to the timing of your meals. You should avoid taking this medicine together with fruit juice and/or drinks containing plant extracts (including herbal teas). During your treatment, your doctor may adjust your dose depending on your blood pressure response.

If you take more Rasilez HCT than you should
If you have accidentally taken too many tablets of this medicine, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasilez HCT
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 you only remember the forgotten dose the next day, 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.

If you stop taking Rasilez HCT
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.

Some side effects can be serious:
A few patients have experienced these serious side effects. **If any of the following occur, tell your doctor straight away:**

- Severe allergic reaction (anaphylactic reaction), allergic reactions (hypersensitivity) and 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). *(rare: may affect up to 1 in 1,000 pople).*
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (signs of liver disorder) *(frequency not known: frequency cannot be estimated from the available data).*

Other side effects may include:
Side effects associated with each individual component cannot be excluded. The adverse reactions previously reported with one of the two active substances (aliskiren and hydrochlorothiazide) of Rasilez HCT and listed below may occur with Rasilez HCT.

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):
- Diarrhoea
- Joint pain (arthralgia)
- High level of potassium in the blood
- Dizziness
- 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

Uncommon (may affect up to 1 in 100 people):
- Low blood pressure
- 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)
- Palpitations
- Cough
- Itching
- Itchy rash (urticarial)
- Increased liver enzymes

Rare (may affect up to 1 in 1,000 people):
- Increased level of creatinine in the blood
- Red skin (erythema)
- 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
- Headache
- Tingling or numbness
- Vision disorder
- Irregular heart beat
- Abdominal discomfort
- Constipation
- 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):
- Skin and lip cancer (Non-melanoma skin cancer)
- Weakness
- Bruising and frequent infections (aplastic anaemia)
- Decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or 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
- Dizziness with spinning sensation
- Shortness of breath

If any of these affect you severely, tell your doctor. You may need to stop Rasilez HCT.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rasilez HCT

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 25°C.
Store 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 Rasilez HCT contains
- The active substances are aliskiren and hydrocholorothiazide.

Rasilez HCT 150 mg/12.5 mg film-coated tablets

- Each tablet contains 150 mg aliskiren (as hemifumarate) and 12.5 mg hydrocholorothiazide. The other ingredients are: Microcrystalline cellulose, crospovidone type A, lactose monohydrate and wheat starch (see section 2 under 'Rasilez HCT contains lactose and wheat starch'), povidone K-30, magnesium stearate, silica colloidal anhydrous, talc, hypromellose substitution type 2910 (3 mPa s), macrogol 4000, titanium dioxide (E171).

Rasilez HCT 150 mg/25 mg film-coated tablets

- Each tablet contains 150 mg aliskiren (as hemifumarate) and 25 mg hydrocholorothiazide. The other ingredients are: Microcrystalline cellulose, crospovidone type A, lactose monohydrate (see section 2), wheat starch (see section 2), povidone K-30, magnesium stearate, silica colloidal anhydrous, talc, hypromellose substitution type 2910 (3 mPa s), macrogol 4000, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172).

Rasilez HCT 300 mg/12.5 mg film-coated tablets

- Each tablet contains 300 mg aliskiren (as hemifumarate) and 12.5 mg hydrocholorothiazide. The other ingredients are: Microcrystalline cellulose, crospovidone type A, lactose monohydrate (see section 2), wheat starch (see section 2), povidone K-30, magnesium stearate, silica colloidal anhydrous, talc, hypromellose substitution type 2910 (3 mPa s), macrogol 400, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172).

Rasilez HCT 300 mg/25 mg film-coated tablets

- Each tablet contains 300 mg aliskiren (as hemifumarate) and 25 mg hydrocholorothiazide. The other ingredients are: Microcrystalline cellulose, crospovidone type A, lactose monohydrate (see section 2), wheat starch (see section 2), povidone K-30, magnesium stearate, silica colloidal anhydrous, talc, hypromellose substitution type 2910 (3 mPa s), macrogol 4000, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172).

What Rasilez HCT looks like and contents of the pack
Rasilez HCT 150 mg/12.5 mg film-coated tablets are white, oval film-coated tablets imprinted with "LCI" on one side and "NVR" on the other.
Rasilez HCT 150 mg/25 mg film-coated tablets are pale yellow, oval film-coated tablets imprinted with "CLL" on one side and "NVR" on the other.
Rasilez HCT 300 mg/12.5 mg film-coated tablets are violet white, oval film-coated tablets imprinted with "CVI" on one side and "NVR" on the other.
Rasilez HCT 300 mg/25 mg film-coated tablets are light yellow, oval film-coated tablets imprinted with "CVV" on one side and "NVR" on the other.

PA/Alu/PVC – Alu blisters
Single-packs containing 7, 14, 28, 30, 50 or 56 tablets.
Multi-packs containing 90 (3 packs of 30), 98 (2 packs of 49) or 280 (20 packs of 14) tablets.

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters
Single-packs containing 7, 14, 28, 30, 50, 56, 90 or 98 tablets.
Single-packs (perforated unit dose blister) containing 56 x 1 tablets.
Multi-packs containing 280 (20 packs of 14) tablets.
Multi-packs (perforated unit dose blister) containing 98 (2 packs of 49 x 1) tablets.

Not all pack sizes or strengths may be available in your country.

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D'Olier Chambers

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Ireland

Manufacturer
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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