ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 150 mg film-coated tablets
Rasilez 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rasilez 150 mg film-coated tablets
Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

Rasilez 300 mg film-coated tablets
Each film-coated tablet contains 300 mg aliskiren (as hemifumarate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Rasilez 150 mg film-coated tablets
Light-pink, biconvex, round tablet, imprinted “IL” on one side and “NVR” on the other side.

Rasilez 300 mg film-coated tablets
Light-red, biconvex, ovaloid tablet, imprinted “IU” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

4.2 Posology and method of administration

Posology

The recommended dose of Rasilez is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.

The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.

Rasilez may be used alone or in combination with other antihypertensive agents with the exception of use in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2) (see sections 4.3, 4.4 and 5.1).

Special populations

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Aliskiren is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2).

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to severe hepatic impairment (see section 5.2).

Elderly patients aged 65 years and over
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
Rasilez is contraindicated in children from birth to less than 2 years. Rasilez 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 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 is not recommended in this population.

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilez 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 substance or to any of the excipients listed in section 6.1.
- History of angioedema with aliskiren.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see section 4.6).
- 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 with an angiotensin converting enzyme inhibitor(ACEI) or an angiotensin II receptor blocker (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

General

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

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).

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

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.

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with aliskiren 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, or the treatment should start under close medical supervision.

Renal impairment

In clinical studies aliskiren has not been investigated in hypertensive patients with severe renal impairment (serum creatinine ≥ 150 µmol/l or 1.70 mg/dl in women and ≥ 177 µmol/l or 2.00 mg/dl in men and/or estimated GFR < 30 ml/min/1.73 m^2), history of dialysis, nephrotic syndrome or renovascular hypertension. It is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2).

As for other medicinal products acting on the renin-angiotensin system, 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 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.

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.

Renal artery stenosis

No controlled clinical data are available on the use of aliskiren 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, treatment 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.

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 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 sections 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

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

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 aliskiren. 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 aliskiren (see section 4.2)

Dual blockade of the RAAS with aliskiren, ARBs or ACEIs
Clinical trial 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-administration 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.

Pharmacokinetic interaction 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 Rasilez. When administered with atorvastatin, steady-state Rasilez AUC and C_{max} increased by 50%. Co-administration of Rasilez had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for Rasilez or these co-administered medicinal products is necessary.

Digoxin and verapamil bioavailability may be slightly decreased by Rasilez.

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 Rasilez bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Rasilez.

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).

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. As for any medicine that acts directly on the RAAS, alsikiren 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). Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, treatment should be discontinued accordingly.

Breast-feeding

It is unknown whether aliskiren/metabolites are excreted in human milk. Aliskiren was secreted in the milk of lactating rats. A risk to the newborns/infants cannot be excluded. Aliskiren should not be used during breast-feeding.

Fertility

There are no clinical data on fertility.

4.7 Effects on ability to drive and use machines

Rasilez 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.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Aliskiren has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over 1 year. The adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1

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

*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

Hypersensitivity reactions including anaphylactic reactions and angioedema
In controlled clinical studies, 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 medicines 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.

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

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

Haemoglobin and haematocrit
Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other 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 week 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 on 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).

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

Limited data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren.

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: C09XA02

Mechanism of action

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

Pharmacodynamic effects

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 (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the differences in effect on PRA are not known at the present time.

Clinical efficacy and safety

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

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

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

patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of aliskiren 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing amlodipine dose to 10 mg, but had a lower incidence of oedema (aliskiren 150 mg/amlodipine 5 mg 2.1% vs. amlodipine 10 mg 11.2%).

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 studies 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).

In obese hypertensive patients who did not adequately respond to HCTZ 25 mg, add-on treatment with aliskiren 300 mg provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan 300 mg or amlodipine 10 mg.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents. 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 re-modelling 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.

Cardiac electrophysiology

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

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 deferred the obligation to submit the results of studies with aliskiren in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce C_{max} by 85% and AUC by 70%. At steady state meals with low fat content reduce C_{max} by 76% and $AUC_{0\text{-}tau}$ by 67% in hypertensive patients. 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

Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4.

Elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 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/non-linearity

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

Characteristics in patients

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

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

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).

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

Elderly patients aged 65 years and over
The AUC is 50% higher in elderly (> 65 years) than in young subjects. Gender, weight and ethnicity have no clinically relevant influence on aliskiren pharmacokinetics.

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 (see section 5.1).

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).

5.3 Preclinical safety data

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

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

Crospovidone, type A
Magnesium stearate
Microcrystalline cellulose
Povidone, K-30
Colloidal anhydrous silica
Hypromellose substitution type 2910 (3 mPa·s)
Macrogol 4000
Talc
Black iron oxide (E 172)
Red iron oxide (E 172)
Titanium dioxide (E 171)

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

Rasilez 150 mg film-coated tablets

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets.
Unit packs containing 56x1 tablets in perforated unit dose blisters.
Multipacks containing 280 (20x14) tablets.
Multipacks containing 98 (2x49x1) tablets in perforated unit dose blisters.

Rasilez 300 mg film-coated tablets

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:
Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets.
Unit packs containing 56x1 tablets in perforated unit dose blisters.
Multipacks containing 280 (20x14) tablets.
Multipacks containing 98 (2x49x1) tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Noden Pharma DAC

D'Olier Chambers
16A D'Olier Street
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Rasilez 150 mg film-coated tablets
EU/1/07/405/021-030

Rasilez 300 mg film-coated tablets
EU/1/07/405/031-040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2007
Date of latest renewal: 22 May 2017

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

Delpharm Milano S.R.L.,
Via Carnevale, 1,
Segrate (MI),
20054,
Italy.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The 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 FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 150 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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 tablets
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/1/07/405/021	14 film-coated tablets
EU/1/07/405/022	28 film-coated tablets
EU/1/07/405/023	30 film-coated tablets
EU/1/07/405/024	50 film-coated tablets
EU/1/07/405/025	56 film-coated tablets
EU/1/07/405/026	56 x 1 film-coated tablet
EU/1/07/405/027	90 film-coated tablets
EU/1/07/405/028	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 150 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

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 150 mg film-coated tablets
aliskiren

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 PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 150 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets. Component of a multipack. Not to be sold separately.
49 x 1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 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/1/07/405/029	98 film-coated tablets (2x49x1)
EU/1/07/405/030	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 150 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 98 (2 packs of 49 x 1) 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/1/07/405/029 98 film-coated tablets (2x49x1)
EU/1/07/405/030 280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 150 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 BOX FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 300 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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 tablets
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/1/07/405/031	14 film-coated tablets
EU/1/07/405/032	28 film-coated tablets
EU/1/07/405/033	30 film-coated tablets
EU/1/07/405/034	50 film-coated tablets
EU/1/07/405/035	56 film-coated tablets
EU/1/07/405/036	56 x1 film-coated tablets
EU/1/07/405/037	90 film-coated tablets
EU/1/07/405/038	98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 300 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

BLISTER
BLISTER (CALENDAR)

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 300 mg film-coated tablets
aliskiren

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 PCTFE/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 300 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets. Component of a multipack. Not to be sold separately.
49 x 1 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 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/1/07/405/039	98 film-coated tablets (2x49x1)
EU/1/07/405/040	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 300 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Rasilez 300 mg film-coated tablets
aliskiren

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (20 packs of 14) film-coated tablets
Multipack: 98 (2 packs of 49 x 1) 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/1/07/405/039	98 film-coated tablets (2x49x1)
EU/1/07/405/040	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilez 300 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 150 mg film-coated tablets
Rasilez 300 mg film-coated tablets
Aliskiren

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 is and what it is used for

This medicine contains an active substance called aliskiren. Aliskiren belongs to a class of medicines called renin inhibitors. Renin inhibitors reduce the amount of angiotensin II the body can produce. Angiotensin II causes blood vessels to tighten, which increases the blood pressure. Reducing the amount of angiotensin II allows the blood vessels to relax, which 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.

2. What you need to know before you take Rasilez

Do not take Rasilez
- if you are allergic to aliskiren or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):
  - angioedema when taking aliskiren.
  - hereditary angioedema.
  - angioedema without any known cause.
- during the last 6 months of pregnancy or if you are breast-feeding, see section “Pregnancy and breastfeeding”.
- 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.

Warnings and precautions
Talk to your doctor before taking Rasilez:
- if you are taking a diuretic (a type of medicine also known as "water" tablets which increases the amount of urine you produce).
- 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 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 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 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).

If you have severe and persistent diarrhoea you should stop taking Rasilez.

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".

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
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 Rasilez shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Other medicines and Rasilez
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Your doctor may need to change your dose and/or to take other precautions if you are taking one of the following medicines:
- medicines that increase the amount of potassium in your blood. These include potassium-sparing diuretics, potassium supplements.
- 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.
- an angiotensin II receptor blocker or an angiotensin converting enzyme inhibitor (see sections "Do not take Rasilez" and "Warnings and precautions").
- ketoconazole, a medicine used to treat fungal infections.
- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat

angina pectoris.
- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs).

Rasilez 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 and breast-feeding
Pregnancy
Do not take this medicine if you are pregnant (see section "Do not take Rasilez"). 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 in early 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 and this can affect your ability to concentrate. Before you drive a vehicle, use machinery, or carry out other activities that require concentration, you should make sure you know how you react to the effects of this medicine.

3. How to take Rasilez

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

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.

The usual starting dose is one 150 mg tablet once daily. The blood pressure lowering effect is present within two weeks 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.

Depending on how you respond to the treatment your doctor may prescribe a higher dose of one 300 mg tablet once daily. Your doctor may prescribe this medicine together with other medicines used to treat high blood pressure.

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 than you should
If you have accidentally taken too many tablets of this medicine, consult a doctor immediately. You may require medical attention.

If you forget to take Rasilez
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. However, if it is almost time for your next dose you should simply take the next tablet at the usual time. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious (frequency not known):
A few patients have experienced these serious side effects. **If any of the following occur, tell your doctor straight away:**
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.

Possible side effects:
Common *(may affect up to 1 in 10 people)*: Diarrhoea, joint pain (arthralgia), high level of potassium in the blood, dizziness.
Uncommon *(may affect up to 1 in 100 people)*: Skin rash (this may also be a sign of allergic reactions or angioedema – see "Rare" side effects below), kidney problems including acute renal failure (severely decreased urine output), swelling of hands, ankles or feet (peripheral oedema), severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions - red skin, blistering of the lips, eyes or mouth, skin peeling, fever), low blood pressure, palpitations, cough, itching, itchy rash (urticaria), increased liver enzymes.
Rare *(may affect up to 1 in 1,000 people)*: increased level of creatinine in the blood, decreased level of haemoglobin in the blood (anaemia), decreased level of red blood cells, red skin (erythema).
Not known *(frequency cannot be estimated from the available data)*: spinning sensation, low level of sodium in the blood, shortness of breath, nausea, vomiting, signs of liver disorder (nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes).

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

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

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. 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 contains
- The active substance is aliskiren (as hemifumarate).

Rasilez 150 mg film-coated tablets
- Each tablet contains 150 mg aliskiren (as hemifumarate). The other ingredients are crospovidone type A, hypromellose substitution type 2910 (3 mPa s), magnesium stearate, macrogol 4000, microcrystalline cellulose, povidone K-30, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

Rasilez 300 mg film-coated tablets
- Each tablet contains 300 mg aliskiren (as hemifumarate). The other ingredients are crospovidone type A, hypromellose substitution type 2910 (3 mPa s), magnesium stearate, macrogol 4000, microcrystalline cellulose, povidone K-30, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

What Rasilez looks like and contents of the pack
Rasilez 150 mg film-coated tablets are light-pink, biconvex round tablets, imprinted “IL” on one side and “NVR” on the other side.

Rasilez 300 mg film-coated tablets are light-red, biconvex, ovaloid tablets, imprinted “IU” on one side and “NVR” on the other side.

Rasilez 150 mg film-coated tablets are available in the following packs:
- Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets
- Unit packs containing 56x1 tablets in perforated unit-dose blisters
- Multipacks containing 280 (20x14) tablets
- Multipacks containing 98 (2x49x1) tablets in perforated unit-dose blisters

Rasilez 300 mg film-coated tablets are available in the following packs:
- Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets
- Unit packs containing 56x1 tablets in perforated unit-dose blisters
- Multipacks containing 280 (20x14) tablets
- Multipacks containing 98 (2x49x1) tablets in perforated unit-dose blisters

Not all pack sizes may be available in your country.

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

Manufacturer
Delpharm Milano S.R.L.,
Via Carnevale, 1,
Segrate (MI),
20054,
Italy.

This leaflet was last revised in 02/2023

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