ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light yellow, convex, ovaloid tablet with a bevelled edge, with "T2" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

4.2 Posology and method of administration

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

The antihypertensive effect is manifested within 1 week and the effect is near maximal at around 4 weeks. If blood pressure remains uncontrolled after 4 to 6 weeks of therapy, the dose may be titrated up to a maximum of 300 mg aliskiren/10 mg amlodipine. Dose should be individualised and adjusted according to the patient's clinical response.

Rasilamlo may be administered with other antihypertensive medicinal products 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).

Posology in patients not adequately controlled with aliskiren or amlodipine monotherapy
Rasilamlo 150 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 150 mg or amlodipine 5 mg alone.

A patient who experiences dose limiting adverse reactions on either component alone may be switched to Rasilamlo containing a lower dose of that component to achieve similar blood pressure reductions.

Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate and in line with the above-mentioned posology, direct change from monotherapy to the fixed combination may be considered.

Special populations

Renal impairment

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (GFR 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively, see sections 4.4 and 5.2). Rasilamlo is not recommended in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2).

Hepatic impairment

Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment; therefore, caution should be exercised when administering Rasilamlo to patients with hepatic impairment.

Elderly people (over 65 years)

There is limited experience with Rasilamlo, in particular in patients aged 75 years or older. Therefore, particular caution should be exercised in these patients. 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 Rasilamlo in children below age 18 have not been established. No data are available.

Rasilamlo 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 because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilamlo should be taken with a light meal once a day, preferably at the same time each day. 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 other dihydropyridine derivatives.
- 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 Rasilamlo with an ACEI or an 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).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- 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, Rasilamlo therapy should be stopped (see section 4.8).

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and 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
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

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

Risk of symptomatic hypotension
Symptomatic hypotension could occur after initiation of treatment with Rasilamlo 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 Rasilamlo, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with Rasilamlo in short-term controlled trials, the incidence of hypotension was low (0.2%).

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. Rasilamlo 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-aldosterone system, caution should be exercised when Rasilamlo 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.

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.

Hepatic impairment
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Caution should be exercised when administering Rasilamlo to patients with hepatic impairment (see sections 4.2 and 5.2).

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

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

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

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

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

Special caution is necessary in patients with a hypersensitivity predisposition.

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

If anaphylactic reactions or angioedema occur, Rasilamlo 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, Rasilamlo 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.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasilamlo interactions
No interaction studies with other medicinal products were performed with Rasilamlo. Therefore, information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

Co-administration of aliskiren and amlodipine does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (C_{max}) of either component in healthy volunteers.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *P-gp potent inhibitors*

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

Not recommended (see section 4.2)
- *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 Rasilamlo. 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 Rasilamlo.

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 trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable.

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

As with other medicinal products acting on the renin-angiotensin-aldosterone system, 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 interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

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

- *Warfarin*

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

- *Food interactions*

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

No interactions

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

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

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

- *CYP450 interactions*

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

- *P-gp substrates or weak inhibitors*

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

- *Organic anion transporting polypeptide (OATP) inhibitors*

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

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

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

- *CYP3A4 inducers*

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

- *Grapefruit juice*

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

- *Dantrolene (infusion)*

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

Effects of amlodipine on other medicinal products

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

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

No interactions

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception in males and females

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

Pregnancy

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

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

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

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

Breast-feeding
It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not recommended for women who are breast-feeding to use Rasilamlo.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasilamlo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

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

4.7 Effects on 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 Rasilamlo.

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Rasilamlo presented below is based on clinical studies performed with Rasilamlo and the known safety profile of the individual components aliskiren and amlodipine. Safety information for Rasilamlo in patients aged 75 years and older is limited.

The most frequent adverse reactions for Rasilamlo are hypotension and peripheral oedema. The adverse reactions previously reported with one of the individual components of Rasilamlo (aliskiren and amlodipine) and included in the tabulated list of adverse reactions may occur with Rasilamlo.

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

Blood and lymphatic system disorders	
Very rare	Leukopenia[am], thrombocytopenia[am]
Immune system disorders	
Rare	Anaphylactic reactions[a], hypersensitivity reactions[a]
Very rare	Allergic reactions[am]
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia[am]
Psychiatric disorders	
Uncommon	Insomnia[am], mood changes (including anxiety)[am], depression[am]
Rare	Confusion[am]
Nervous system disorders	
Common	Somnolence[am], headache (especially at the beginning of treatment)[am]
Uncommon	Tremor[am], dysgeusia[am], syncope[am], hypoesthesia[am], paraesthesia[am]
Very rare	Hypertonia[am], peripheral neuropathy[am]
Eye disorders	
Uncommon	Visual disturbance (including diplopia)[am]
Ear and labyrinth disorders	
Uncommon	Tinnitus[am]
Not known	Vertigo[a]
Cardiac disorders	
Common	Dizziness[a,am], palpitations[a,am], peripheral oedema[c,a,am]*
Very rare	Myocardial infarction[am], arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation)[am]
Vascular disorders	
Common	Flushing[am], hypotension[c,a,am]
Very rare	Vasculitis[am]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea[a, am], rhinitis[am], cough[a,am]
Gastrointestinal disorders	
Common	Diarrhoea[a], abdominal pain[am], nausea[a,am]
Uncommon	Vomiting[a,am], dyspepsia[am], altered bowel habits (including diarrhoea and constipation)[am], dry mouth[am]
Very rare	Pancreatitis[am], gastritis[am], gingival hyperplasia[am]
Hepatobiliary disorders	
Very rare	Hepatitis[a,am], jaundice[a,am], hepatic enzymes increased (mostly consistent with cholestasis)[am]
Not known	Liver disorder[a,]**, liver failure[a,]***

Skin and subcutaneous tissue disorders	
Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome[a], toxic epidermal necrolysis (TEN)[a], oral mucosal reactions[a], rash[a,am], pruritus[a,am], urticaria[a,am], alopecia[am], purpura[am], skin decolouration[am], hyperhidrosis[am], exanthema[am]
Rare	Angioedema[a], erythema[a]
Very rare	Erythema multiforme[am], exfoliative dermatitis[am], Stevens-Johnson syndrome[am], Quincke oedema[am], photosensitivity[am]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia[a,am], ankle swelling[am]
Uncommon	Myalgia[am], muscle cramps[am], back pain[am]
Renal and urinary disorders	
Uncommon	Acute renal failure[a], renal impairment[a], micturition disorder[am], nocturia[am], increased urinary frequency[am]
Reproductive system and breast disorders	
Uncommon	Impotence[am], gynaecomastia[am]
General disorders and administration site conditions	
Common	Fatigue[am]
Uncommon	Chest pain[am], asthenia[am], pain[am], malaise[am]
Investigations	
Common	Hyperkalaemia[a]
Uncommon	Liver enzyme increased[a], weight increase[am], weight decrease[am]
Rare	Haemoglobin decreased[a], haematocrit decreased[a], blood creatinine increased[a]
Not known	Hyponatraemia[a]

[c] Adverse reaction observed with Rasilamlo;
[a] Adverse reaction observed with monotherapy with aliskiren;
[am] Adverse reaction observed with monotherapy with amlodipine;
* Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The most frequently reported adverse reaction for Rasilamlo in clinical trials was peripheral oedema, which occurred at a frequency lower than or equal to that of the corresponding amlodipine doses, but higher than with aliskiren;
** 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.

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

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

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

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

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

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

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

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

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

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

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

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

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

Amlodipine
Exceptional cases of extrapyramidal syndrome have been reported.

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
There is no experience of overdose with Rasilamlo. The most likely manifestation of overdose for Rasilamlo would be hypotension, related to the antihypertensive effect of aliskiren and amlodipine.

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

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

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin inhibitors, ATC code: C09XA53

Rasilamlo combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the class of direct renin inhibitors and amlodipine belongs to the calcium antagonist class.

Rasilamlo

The use of combined treatment with aliskiren and amlodipine arises from the actions of these two medicinal products on different but complementary systems that regulate blood pressure. Calcium channel blockers act to prevent the influx of calcium into the vascular smooth muscle cells in the vessel wall, thereby preventing smooth muscle cell contraction and vasoconstriction. Renin inhibitors suppress the enzymatic activity of renin, and thereby block the formation of Angiotensin II, the major effector molecule of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II causes vasoconstriction and sodium and water reabsorption. Thus, amlodipine directly inhibits vasoconstriction and reduces vascular resistance, while aliskiren, by controlling Ang II production, can also inhibit vasoconstriction but additionally shifts water and sodium balance toward levels necessary for normotensive conditions. The combined action of aliskiren and amlodipine on these two central blood pressure-regulating factors (vasoconstriction and RAAS-mediated hypertensive effects) results in more effective antihypertensive effects than seen with monotherapy.

Rasilamlo was studied in a number of active and placebo-controlled trials and long-term trials which included a total of 5,570 hypertensive patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

In hypertensive patients not controlled by the component monotherapies, once-daily administration of Rasilamlo provided dose-dependent clinically meaningful reductions in both systolic and diastolic blood pressure.

When given to patients whose blood pressure was not adequately controlled by either aliskiren or amlodipine, Rasilamlo results in greater blood pressure reductions after one week of treatment than the component monotherapies and a near-maximal effect is achieved after four weeks of therapy.

In a study in 820 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/amlodipine 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 18.0/13.1 mmHg, which were statistically significantly greater than aliskiren 300 mg monotherapy. The combination at a dose of 300 mg/5 mg also showed statistically significantly greater blood pressure reduction than aliskiren 300 mg monotherapy. In a subset of 584 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 7.9/4.8 mmHg and 11.7/7.7 mmHg for the 300/5 mg and 300/10 mg strengths respectively compared to aliskiren 300 mg (the subset constitutes patients without aberrant readings, defined as difference in systolic blood pressure (SBP) ≥10 mmHg at baseline or endpoint).

In a study in 847 randomised patients not adequately responsive to amlodipine 10 mg treatment, the combination of aliskiren/amlodipine 150 mg/10 mg and 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 11.0/9.0 mmHg and 14.4/11.0 mmHg respectively, which were statistically greater than for amlodipine 10 mg monotherapy. In a subset of 549 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 4.0/2.2 mmHg and 7.6/4.7 mmHg for the 150/10 mg and 300/10 mg strengths respectively compared to amlodipine 10 mg (the subset constitutes patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

In a study in 545 randomised patients not adequately responsive to 5 mg amlodipine, the combination of aliskiren 150 mg/amlodipine 5 mg resulted in greater blood pressure reduction than those patients remaining on amlodipine 5 mg.

In an 8-week randomised, double-blind, placebo-controlled, parallel group factorial study in 1,688 randomised patients with mild to moderate hypertension, treatment with Rasilamlo at doses from 150 mg/5 mg to 300 mg/10 mg produced dose-dependent clinically meaningful mean blood pressure reductions (systolic/diastolic) ranging between 20.6/14.0 mmHg and 23.9/16.5 mmHg, respectively, compared to 15.4/10.2 mmHg for aliskiren 300 mg, 21.0/13.8 mmHg for amlodipine 10 mg and 6.8/5.4 mmHg with placebo in a population of patients with mean baseline blood pressure of 157.3/99.7 mmHg. These were statistically significant versus placebo and aliskiren for all doses. The blood pressure reductions with the combination were maintained throughout the entire 24-hour dose interval. In a subset of 1,069 patients, Rasilamlo produced mean blood pressure reductions (systolic/diastolic) ranging between 20.6/13.6 mmHg and 24.2/17.3 mmHg (the subset of patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

The safety of Rasilamlo has been evaluated in studies of up to one year duration.

The effects of Rasilamlo on all cause and cardiovascular mortality and on cardiovascular morbidity and target organ damage are currently unknown.

Rasilamlo has been administered to more than 2,800 patients in completed clinical trials, including 372 patients for one year or more. Treatment with Rasilamlo at doses up to 300 mg/10 mg had an overall incidence of adverse experiences similar to the component monotherapies. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. There were no new adverse reactions which occurred specifically with Rasilamlo in addition to those known to be associated with the individual monotherapies. In a double-blind, randomised placebo-controlled study in 1,688 patients with mild or moderate hypertension, discontinuation of therapy due to a clinical adverse event occurred in 1.7% of patients treated with Rasilamlo versus 1.5% of patients given placebo.

Aliskiren

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

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

Hypertension

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

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

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

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

In 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.

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

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

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

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

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. 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.

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

No long-term efficacy data for aliskiren in patients with heart failure are currently available.

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasilamlo 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 $_{0\text{-tau}}$ by 67% in hypertensive patients. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

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 (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

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

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients aged 6 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).

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 "Transporters" above and sections 4.2, 4.4 and 5.3).

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

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

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

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

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

Aliskiren/amlodipine

Following oral administration of Rasilamlo, the median peak plasma concentration time is within 3 hours for aliskiren and 8 hours for amlodipine. The rate and extent of absorption of Rasilamlo are similar in fasting state to those of aliskiren and amlodipine when administered as individual monotherapies. A bioequivalence study under light meal conditions has not been conducted for Rasilamlo.

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

Characteristics in patients

Aliskiren

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

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.

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 aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2).

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

The pharmacokinetics of 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.

Amlodipine

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

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

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

5.3 Preclinical safety data

Aliskiren

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

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

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

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

Juvenile Animal Studies

A repeat-dose toxicity study was conducted in juvenile rats 8 days post-partum for 4 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. High acute mortality (within hours) and severe morbidity were observed at 100 and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose (MRHD) on mg/m^2 basis assuming a 60 kg adult patient) with no cause of death established and occurring without signs or prodromal symptoms. The ratio of lethal dose of 100 mg/kg/day and no-observed-adverse-effect-level (NOAEL) of 30 mg/kg/day is unexpectedly low.

Another repeat-dose toxicity study was conducted in juvenile rats 14 days post-partum for 8 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. Delayed mortality was observed at 300 mg/kg/day (8.5-fold the MRHD on mg/m2 basis assuming a 60 kg adult patient) with no cause of death established.

For the surviving juvenile rats, no effects on behavioural or reproductive performance were observed.

Plasma aliskiren exposure (AUC) in rats aged 8 days was nearly 4-fold higher than that in rats aged 14 days at 100 mg/kg/day. Plasma aliskiren exposure in rats aged 14 days was between 85- and 387-fold higher than that in adult rats aged 64 days.

A single dose study was conducted in juvenile rats aged 14, 21, 24, 28, 31 or 36 days post-partum. No mortality or significant toxicity was observed. The plasma exposure was approximately 100-fold higher in rats aged 14 days and 3-fold higher in rats aged 21 days compared to adult rats.

A mechanistic study was conducted to investigate the relationship between age, aliskiren exposure and MDR1 and OATP2 expression maturation in rats. The results showed that developmental changes of aliskiren exposure correlated with the ontogeny of transporter maturation in jejunum, liver, kidney and brain.

The pharmacokinetics of aliskiren was evaluated in rats aged from 8 to 28 days after intravenous administration of aliskiren 3 mg/kg. The clearance of aliskiren increased in an age-dependent manner. Clearance in rats aged 8 or 14 days was similar, but at these ages the clearance was only about 23% of clearance in rats aged 21 days and 16% of clearance in rats aged 28 days.

These studies indicate that excessive aliskiren exposure (>400-fold higher in 8-day old rats compared with adult rats) and high acute toxicity in juvenile rats are caused by immature MDR1, which suggests that in paediatric patients with immature MDR1, there is a potential for aliskiren overexposure (see sections 4.2, 4.3 and 5.2).

Amlodipine

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

Reproductive toxicology

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

Impairment of fertility

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

Carcinogenesis, mutagenesis

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

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

*Based on patient weight of 50 kg

Rasilamlo

Preclinical safety studies have demonstrated that the combination of aliskiren and amlodipine was well tolerated in rats. The findings from the 2- and 13-week oral toxicity studies in rats were consistent with those of aliskiren and amlodipine when both active substances are administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PCTFE – Alu blisters:
18 months

PA/Alu/PVC – Alu blisters:
18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets
Multi-packs containing 280 tablets (20 packs of 14)

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

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multi-packs containing 98 tablets (2 packs of 49) and 280 tablets (20 packs of 14)

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/001-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 10 mg amlodipine (as besylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, convex, ovaloid tablet with a bevelled edge, with "T7" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

4.2 Posology and method of administration

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

The antihypertensive effect is manifested within 1 week and the effect is near maximal at around 4 weeks. If blood pressure remains uncontrolled after 4 to 6 weeks of therapy, the dose may be titrated up to a maximum of 300 mg aliskiren/10 mg amlodipine. Dose should be individualised and adjusted according to the patient's clinical response.

Rasilamlo may be administered with other antihypertensive medicinal products 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).

Posology in patients not adequately controlled with aliskiren or amlodipine monotherapy
Rasilamlo 150 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg alone or with Rasilamlo 150 mg/5 mg.

A patient who experiences dose limiting adverse reactions on either component alone may be switched to Rasilamlo containing a lower dose of that component to achieve similar blood pressure reductions.

Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate and in line with the above-mentioned posology, direct change from monotherapy to the fixed combination may be considered.

Special populations

Renal impairment

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (GFR 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively, see sections 4.4 and 5.2). Rasilamlo is not recommended in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2).

Hepatic impairment

Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment; therefore, caution should be exercised when administering Rasilamlo to patients with hepatic impairment.

Elderly people (over 65 years)

There is limited experience with Rasilamlo, in particular in patients aged 75 years or older. Therefore, particular caution should be exercised in these patients. 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 Rasilamlo in children below age 18 have not been established. No data are available.

Rasilamlo 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 because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilamlo should be taken with a light meal once a day, preferably at the same time each day. 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 other dihydropyridine derivatives.
- 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 Rasilamlo with an ACEI or an 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).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- 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, Rasilamlo therapy should be stopped (see section 4.8).

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and 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
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

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

Risk of symptomatic hypotension
Symptomatic hypotension could occur after initiation of treatment with Rasilamloin 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 Rasilamlo, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with Rasilamlo in short-term controlled trials, the incidence of hypotension was low (0.2%).

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. Rasilamlo 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-aldosterone system, caution should be exercised when Rasilamlo 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.

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.

Hepatic impairment
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Caution should be exercised when administering Rasilamlo to patients with hepatic impairment (see sections 4.2 and 5.2).

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

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

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

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

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

Special caution is necessary in patients with a hypersensitivity predisposition.

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

If anaphylactic reactions or angioedema occur, Rasilamlo 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, Rasilamlo 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.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasilamlo interactions
No interaction studies with other medicinal products were performed with Rasilamlo. Therefore, information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

Co-administration of aliskiren and amlodipine does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (C_{max}) of either component in healthy volunteers.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *P-gp potent inhibitors*

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

Not recommended (see section 4.2)
- *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 Rasilamlo. 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 Rasilamlo.

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 trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable.

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

As with other medicinal products acting on the renin-angiotensin-aldosterone system, 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 interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

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

- *Warfarin*

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

- *Food interactions*

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

No interactions

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

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

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

- *CYP450 interactions*

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

- *P-gp substrates or weak inhibitors*

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

- *Organic anion transporting polypeptide (OATP) inhibitors*

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

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

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

- *CYP3A4 inducers*

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

- *Grapefruit juice*

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

- *Dantrolene (infusion)*

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

Effects of amlodipine on other medicinal products

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

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

No interactions

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception in males and females

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

Pregnancy

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

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

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

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

Breast-feeding
It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not recommended for women who are breast-feeding to use Rasilamlo.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasilamlo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

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

4.7 Effects on 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 Rasilamlo.

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Rasilamlo presented below is based on clinical studies performed with Rasilamlo and the known safety profile of the individual components aliskiren and amlodipine. Safety information for Rasilamlo in patients aged 75 years and older is limited.

The most frequent adverse reactions for Rasilamlo are hypotension and peripheral oedema. The adverse reactions previously reported with one of the individual components of Rasilamlo (aliskiren and amlodipine) and included in the tabulated list of adverse reactions may occur with Rasilamlo.

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

Blood and lymphatic system disorders	
Very rare	Leukopenia[am], thrombocytopenia[am]
Immune system disorders	
Rare	Anaphylactic reactions[a], hypersensitivity reactions[a]
Very rare	Allergic reactions[am]
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia[am]
Psychiatric disorders	
Uncommon	Insomnia[am], mood changes (including anxiety)[am], depression[am]
Rare	Confusion[am]
Nervous system disorders	
Common	Somnolence[am], headache (especially at the beginning of treatment)[am]
Uncommon	Tremor[am], dysgeusia[am], syncope[am], hypoesthesia[am], paraesthesia[am]
Very rare	Hypertonia[am], peripheral neuropathy[am]
Eye disorders	
Uncommon	Visual disturbance (including diplopia)[am]
Ear and labyrinth disorders	
Uncommon	Tinnitus[am]
Not known	Vertigo[a]
Cardiac disorders	
Common	Dizziness[a,am], palpitations[a,am], peripheral oedema[c,a,am]*
Very rare	Myocardial infarction[am], arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation)[am]
Vascular disorders	
Common	Flushing[am], hypotension[c,a,am]
Very rare	Vasculitis[am]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea[a, am], rhinitis[am], cough[a,am]
Gastrointestinal disorders	
Common	Diarrhoea[a], abdominal pain[am], nausea[a,am]
Uncommon	Vomiting[a,am], dyspepsia[am], altered bowel habits (including diarrhoea and constipation)[am], dry mouth[am]
Very rare	Pancreatitis[am], gastritis[am], gingival hyperplasia[am]
Hepatobiliary disorders	
Very rare	Hepatitis[a,am], jaundice[a,am], hepatic enzymes increased (mostly consistent with cholestasis)[am]
Not known	Liver disorder[a,]**, liver failure[a,]***

Skin and subcutaneous tissue disorders	
Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome[a], toxic epidermal necrolysis (TEN)[a], oral mucosal reactions[a], rash[a,am], pruritus[a,am], urticaria[a,am], alopecia[am], purpura[am], skin decolouration[am], hyperhidrosis[am], exanthema[am]
Rare	Angioedema[a], erythema[a]
Very rare	Erythema multiforme[am], exfoliative dermatitis[am], Stevens-Johnson syndrome[am], Quincke oedema[am], photosensitivity[am]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia[a,am], ankle swelling[am]
Uncommon	Myalgia[am], muscle cramps[am], back pain[am]
Renal and urinary disorders	
Uncommon	Acute renal failure[a], renal impairment[a], micturition disorder[am], nocturia[am], increased urinary frequency[am]
Reproductive system and breast disorders	
Uncommon	Impotence[am], gynaecomastia[am]
General disorders and administration site conditions	
Common	Fatigue[am]
Uncommon	Chest pain[am], asthenia[am], pain[am], malaise[am]
Investigations	
Common	Hyperkalaemia[a]
Uncommon	Liver enzyme increased[a], weight increase[am], weight decrease[am]
Rare	Haemoglobin decreased[a], haematocrit decreased[a], blood creatinine increased[a]
Not known	Hyponatraemia[a]

[c] Adverse reaction observed with Rasilamlo;
[a] Adverse reaction observed with monotherapy with aliskiren;
[am] Adverse reaction observed with monotherapy with amlodipine;
* Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The most frequently reported adverse reaction for Rasilamlo in clinical trials was peripheral oedema, which occurred at a frequency lower than or equal to that of the corresponding amlodipine doses, but higher than with aliskiren;
** 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.

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

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

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

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

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

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

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

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

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

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

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

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

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

Amlodipine
Exceptional cases of extrapyramidal syndrome have been reported.

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
There is no experience of overdose with Rasilamlo. The most likely manifestation of overdose for Rasilamlo would be hypotension, related to the antihypertensive effect of aliskiren and amlodipine.

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

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

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin inhibitors, ATC code: C09XA53

Rasilamlo combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the class of direct renin inhibitors and amlodipine belongs to the calcium antagonist class.

Rasilamlo

The use of combined treatment with aliskiren and amlodipine arises from the actions of these two medicinal products on different but complementary systems that regulate blood pressure. Calcium channel blockers act to prevent the influx of calcium into the vascular smooth muscle cells in the vessel wall, thereby preventing smooth muscle cell contraction and vasoconstriction. Renin inhibitors suppress the enzymatic activity of renin, and thereby block the formation of Angiotensin II, the major effector molecule of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II causes vasoconstriction and sodium and water reabsorption. Thus, amlodipine directly inhibits vasoconstriction and reduces vascular resistance, while aliskiren, by controlling Ang II production, can also inhibit vasoconstriction but additionally shifts water and sodium balance toward levels necessary for normotensive conditions. The combined action of aliskiren and amlodipine on these two central blood pressure-regulating factors (vasoconstriction and RAAS-mediated hypertensive effects) results in more effective antihypertensive effects than seen with monotherapy.

Rasilamlo was studied in a number of active and placebo-controlled trials and long-term trials which included a total of 5,570 hypertensive patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

In hypertensive patients not controlled by the component monotherapies, once-daily administration of Rasilamlo provided dose-dependent clinically meaningful reductions in both systolic and diastolic blood pressure.

When given to patients whose blood pressure was not adequately controlled by either aliskiren or amlodipine, Rasilamlo results in greater blood pressure reductions after one week of treatment than the component monotherapies and a near-maximal effect is achieved after four weeks of therapy.

In a study in 820 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/amlodipine 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 18.0/13.1 mmHg, which were statistically significantly greater than aliskiren 300 mg monotherapy. The combination at a dose of 300 mg/5 mg also showed statistically significantly greater blood pressure reduction than aliskiren 300 mg monotherapy. In a subset of 584 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 7.9/4.8 mmHg and 11.7/7.7 mmHg for the 300/5 mg and 300/10 mg strengths respectively compared to aliskiren 300 mg (the subset constitutes patients without aberrant readings, defined as difference in systolic blood pressure (SBP) ≥10 mmHg at baseline or endpoint).

In a study in 847 randomised patients not adequately responsive to amlodipine 10 mg treatment, the combination of aliskiren/amlodipine 150 mg/10 mg and 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 11.0/9.0 mmHg and 14.4/11.0 mmHg respectively, which were statistically greater than for amlodipine 10 mg monotherapy. In a subset of 549 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 4.0/2.2 mmHg and 7.6/4.7 mmHg for the 150/10 mg and 300/10 mg strengths respectively compared to amlodipine 10 mg (the subset constitutes patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

In a study in 545 randomised patients not adequately responsive to 5 mg amlodipine, the combination of aliskiren 150 mg/amlodipine 5 mg resulted in greater blood pressure reduction than those patients remaining on amlodipine 5 mg.

In an 8-week randomised, double-blind, placebo-controlled, parallel group factorial study in 1,688 randomised patients with mild to moderate hypertension, treatment with Rasilamlo at doses from 150 mg/5 mg to 300 mg/10 mg produced dose-dependent clinically meaningful mean blood pressure reductions (systolic/diastolic) ranging between 20.6/14.0 mmHg and 23.9/16.5 mmHg, respectively, compared to 15.4/10.2 mmHg for aliskiren 300 mg, 21.0/13.8 mmHg for amlodipine 10 mg and 6.8/5.4 mmHg with placebo in a population of patients with mean baseline blood pressure of 157.3/99.7 mmHg. These were statistically significant versus placebo and aliskiren for all doses. The blood pressure reductions with the combination were maintained throughout the entire 24-hour dose interval. In a subset of 1,069 patients, Rasilamlo produced mean blood pressure reductions (systolic/diastolic) ranging between 20.6/13.6 mmHg and 24.2/17.3 mmHg (the subset of patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

The safety of Rasilamlo has been evaluated in studies of up to one year duration.

The effects of Rasilamlo on all cause and cardiovascular mortality and on cardiovascular morbidity and target organ damage are currently unknown.

Rasilamlo has been administered to more than 2,800 patients in completed clinical trials, including 372 patients for one year or more. Treatment with Rasilamlo at doses up to 300 mg/10 mg had an overall incidence of adverse experiences similar to the component monotherapies. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. There were no new adverse reactions which occurred specifically with Rasilamlo in addition to those known to be associated with the individual monotherapies. In a double-blind, randomised placebo-controlled study in 1,688 patients with mild or moderate hypertension, discontinuation of therapy due to a clinical adverse event occurred in 1.7% of patients treated with Rasilamlo versus 1.5% of patients given placebo.

Aliskiren

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

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

Hypertension

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

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

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

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

In 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.

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

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

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

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

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. 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.

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

No long-term efficacy data for aliskiren in patients with heart failure are currently available.

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasilamlo 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 $AUC_{0\text{-}tau}$ by 67% in hypertensive patients. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

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 (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

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

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients aged 6 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).

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 "Transporters" above and sections 4.2, 4.4 and 5.3).

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

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

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

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

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

Aliskiren/amlodipine

Following oral administration of Rasilamlo, the median peak plasma concentration time is within 3 hours for aliskiren and 8 hours for amlodipine. The rate and extent of absorption of Rasilamlo are similar in fasting state to those of aliskiren and amlodipine when administered as individual monotherapies. A bioequivalence study under light meal conditions has not been conducted for Rasilamlo.

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

Characteristics in patients

Aliskiren

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

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.

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 aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2).

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

The pharmacokinetics of 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.

Amlodipine

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

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

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

5.3 Preclinical safety data

Aliskiren

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

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

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

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

Juvenile Animal Studies

A repeat-dose toxicity study was conducted in juvenile rats 8 days post-partum for 4 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. High acute mortality (within hours) and severe morbidity were observed at 100 and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose (MRHD) on mg/m^2 basis assuming a 60 kg adult patient) with no cause of death established and occurring without signs or prodromal symptoms. The ratio of lethal dose of 100 mg/kg/day and no-observed-adverse-effect-level (NOAEL) of 30 mg/kg/day is unexpectedly low.

Another repeat-dose toxicity study was conducted in juvenile rats 14 days post-partum for 8 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. Delayed mortality was observed at 300 mg/kg/day (8.5-fold the MRHD on mg/m2 basis assuming a 60 kg adult patient) with no cause of death established.

For the surviving juvenile rats, no effects on behavioural or reproductive performance were observed.

Plasma aliskiren exposure (AUC) in rats aged 8 days was nearly 4-fold higher than that in rats aged 14 days at 100 mg/kg/day. Plasma aliskiren exposure in rats aged 14 days was between 85- and 387-fold higher than that in adult rats aged 64 days.

A single dose study was conducted in juvenile rats aged 14, 21, 24, 28, 31 or 36 days post-partum. No mortality or significant toxicity was observed. The plasma exposure was approximately 100-fold higher in rats aged 14 days and 3-fold higher in rats aged 21 days compared to adult rats.

A mechanistic study was conducted to investigate the relationship between age, aliskiren exposure and MDR1 and OATP2 expression maturation in rats. The results showed that developmental changes of aliskiren exposure correlated with the ontogeny of transporter maturation in jejunum, liver, kidney and brain.

The pharmacokinetics of aliskiren was evaluated in rats aged from 8 to 28 days after intravenous administration of aliskiren 3 mg/kg. The clearance of aliskiren increased in an age-dependent manner. Clearance in rats aged 8 or 14 days was similar, but at these ages the clearance was only about 23% of clearance in rats aged 21 days and 16% of clearance in rats aged 28 days.

These studies indicate that excessive aliskiren exposure (>400-fold higher in 8-day old rats compared with adult rats) and high acute toxicity in juvenile rats are caused by immature MDR1, which suggests that in paediatric patients with immature MDR1, there is a potential for aliskiren overexposure (see sections 4.2, 4.3 and 5.2).

Amlodipine

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

Reproductive toxicology

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

Impairment of fertility

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

Carcinogenesis, mutagenesis

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

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

*Based on patient weight of 50 kg

Rasilamlo

Preclinical safety studies have demonstrated that the combination of aliskiren and amlodipine was well tolerated in rats. The findings from the 2- and 13-week oral toxicity studies in rats were consistent with those of aliskiren and amlodipine when both active substances are administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PCTFE – Alu blisters:
18 months

PA/Alu/PVC – Alu blisters:
18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets
Multi-packs containing 280 tablets (20 packs of 14)

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

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multi-packs containing 98 tablets (2 packs of 49) and 280 tablets (20 packs of 14)

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/015-028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Dark yellow, convex, ovaloid tablet with a bevelled edge, with "T11" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

4.2 Posology and method of administration

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

The antihypertensive effect is manifested within 1 week and the effect is near maximal at around 4 weeks. If blood pressure remains uncontrolled after 4 to 6 weeks of therapy, the dose may be titrated up to a maximum of 300 mg aliskiren/10 mg amlodipine. Dose should be individualised and adjusted according to the patient's clinical response.

Rasilamlo may be administered with other antihypertensive medicinal products 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).

Posology in patients not adequately controlled with aliskiren or amlodipine monotherapy
Rasilamlo 300 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg alone or with Rasilamlo 150 mg/5 mg.

A patient who experiences dose limiting adverse reactions on either component alone may be switched to Rasilamlo containing a lower dose of that component to achieve similar blood pressure reductions.

Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate and in line with the above-mentioned posology, direct change from monotherapy to the fixed combination may be considered.

Special populations

Renal impairment

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (GFR 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively, see sections 4.4 and 5.2). Rasilamlo is not recommended in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2).

Hepatic impairment

Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment; therefore, caution should be exercised when administering Rasilamlo to patients with hepatic impairment.

Elderly people (over 65 years)

There is limited experience with Rasilamlo, in particular in patients aged 75 years or older. Therefore, particular caution should be exercised in these patients. 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 Rasilamlo in children below age 18 have not been established. No data are available.

Rasilamlo 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 because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilamlo should be taken with a light meal once a day, preferably at the same time each day. 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 other dihydropyridine derivatives.
- 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 Rasilamlo with an ACEI or an 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).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- 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, Rasilamlo therapy should be stopped (see section 4.8).

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and 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
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

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

Risk of symptomatic hypotension
Symptomatic hypotension could occur after initiation of treatment with Rasilamloin 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 the administration of Rasilamlo, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with Rasilamlo in short-term controlled trials, the incidence of hypotension was low (0.2%).

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. Rasilamlo 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-aldosterone system, caution should be exercised when Rasilamlo 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.

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.

Hepatic impairment
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Caution should be exercised when administering Rasilamlo to patients with hepatic impairment (see sections 4.2 and 5.2).

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

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

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

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

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

Special caution is necessary in patients with a hypersensitivity predisposition.

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

If anaphylactic reactions or angioedema occur, Rasilamlo 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, Rasilamlo 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.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasilamlo interactions
No interaction studies with other medicinal products were performed with Rasilamlo. Therefore, information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

Co-administration of aliskiren and amlodipine does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (C_{max}) of either component in healthy volunteers.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *P-gp potent inhibitors*

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

Not recommended (see section 4.2)
- *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 Rasilamlo. 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 Rasilamlo.

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 trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable.

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

As with other medicinal products acting on the renin-angiotensin-aldosterone system, 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 interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

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

- *Warfarin*

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

- *Food interactions*

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

No interactions

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

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

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

- *CYP450 interactions*

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

- *P-gp substrates or weak inhibitors*

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

- *Organic anion transporting polypeptide (OATP) inhibitors*

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

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

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

- *CYP3A4 inducers*

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

- *Grapefruit juice*

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

- *Dantrolene (infusion)*

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

Effects of amlodipine on other medicinal products

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

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

No interactions

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception in males and females

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

Pregnancy

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

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

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

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

Breast-feeding
It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not recommended for women who are breast-feeding to use Rasilamlo.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasilamlo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

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

4.7 Effects on 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 Rasilamlo.

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Rasilamlo presented below is based on clinical studies performed with Rasilamlo and the known safety profile of the individual components aliskiren and amlodipine. Safety information for Rasilamlo in patients aged 75 years and older is limited.

The most frequent adverse reactions for Rasilamlo are hypotension and peripheral oedema. The adverse reactions previously reported with one of the individual components of Rasilamlo (aliskiren and amlodipine) and included in the tabulated list of adverse reactions may occur with Rasilamlo.

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

Blood and lymphatic system disorders	
Very rare	Leukopenia[am], thrombocytopenia[am]
Immune system disorders	
Rare	Anaphylactic reactions[a], hypersensitivity reactions[a]
Very rare	Allergic reactions[am]
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia[am]
Psychiatric disorders	
Uncommon	Insomnia[am], mood changes (including anxiety)[am], depression[am]
Rare	Confusion[am]
Nervous system disorders	
Common	Somnolence[am], headache (especially at the beginning of treatment)[am]
Uncommon	Tremor[am], dysgeusia[am], syncope[am], hypoesthesia[am], paraesthesia[am]
Very rare	Hypertonia[am], peripheral neuropathy[am]
Eye disorders	
Uncommon	Visual disturbance (including diplopia)[am]
Ear and labyrinth disorders	
Uncommon	Tinnitus[am]
Not known	Vertigo[a]
Cardiac disorders	
Common	Dizziness[a,am], palpitations[a,am], peripheral oedema[c,a,am]*
Very rare	Myocardial infarction[am], arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation)[am]
Vascular disorders	
Common	Flushing[am], hypotension[c,a,am]
Very rare	Vasculitis[am]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea[a, am], rhinitis[am], cough[a,am]
Gastrointestinal disorders	
Common	Diarrhoea[a], abdominal pain[am], nausea[a,am]
Uncommon	Vomiting[a,am], dyspepsia[am], altered bowel habits (including diarrhoea and constipation)[am], dry mouth[am]
Very rare	Pancreatitis[am], gastritis[am], gingival hyperplasia[am]
Hepatobiliary disorders	
Very rare	Hepatitis[a,am], jaundice[a,am], hepatic enzymes increased (mostly consistent with cholestasis)[am]
Not known	Liver disorder[a,]**, liver failure[a,]***

Skin and subcutaneous tissue disorders	
Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome[a], toxic epidermal necrolysis (TEN)[a], oral mucosal reactions[a], rash[a,am], pruritus[a,am], urticaria[a,am], alopecia[am], purpura[am], skin decolouration[am], hyperhidrosis[am], exanthema[am]
Rare	Angioedema[a], erythema[a]
Very rare	Erythema multiforme[am], exfoliative dermatitis[am], Stevens-Johnson syndrome[am], Quincke oedema[am], photosensitivity[am]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia[a,am], ankle swelling[am]
Uncommon	Myalgia[am], muscle cramps[am], back pain[am]
Renal and urinary disorders	
Uncommon	Acute renal failure[a], renal impairment[a], micturition disorder[am], nocturia[am], increased urinary frequency[am]
Reproductive system and breast disorders	
Uncommon	Impotence[am], gynaecomastia[am]
General disorders and administration site conditions	
Common	Fatigue[am]
Uncommon	Chest pain[am], asthenia[am], pain[am], malaise[am]
Investigations	
Common	Hyperkalaemia[a]
Uncommon	Liver enzyme increased[a], weight increase[am], weight decrease[am]
Rare	Haemoglobin decreased[a], haematocrit decreased[a], blood creatinine increased[a]
Not known	Hyponatraemia[a]

[c] Adverse reaction observed with Rasilamlo;
[a] Adverse reaction observed with monotherapy with aliskiren;
[am] Adverse reaction observed with monotherapy with amlodipine;
* Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The most frequently reported adverse reaction for Rasilamlo in clinical trials was peripheral oedema, which occurred at a frequency lower than or equal to that of the corresponding amlodipine doses, but higher than with aliskiren;
** 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.

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

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

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

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

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

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

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

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

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

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

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

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

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

Amlodipine
Exceptional cases of extrapyramidal syndrome have been reported.

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
There is no experience of overdose with Rasilamlo. The most likely manifestation of overdose for Rasilamlo would be hypotension, related to the antihypertensive effect of aliskiren and amlodipine.

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

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

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin inhibitors, ATC code: C09XA53

Rasilamlo combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the class of direct renin inhibitors and amlodipine belongs to the calcium antagonist class.

Rasilamlo

The use of combined treatment with aliskiren and amlodipine arises from the actions of these two medicinal products on different but complementary systems that regulate blood pressure. Calcium channel blockers act to prevent the influx of calcium into the vascular smooth muscle cells in the vessel wall, thereby preventing smooth muscle cell contraction and vasoconstriction. Renin inhibitors suppress the enzymatic activity of renin, and thereby block the formation of Angiotensin II, the major effector molecule of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II causes vasoconstriction and sodium and water reabsorption. Thus, amlodipine directly inhibits vasoconstriction and reduces vascular resistance, while aliskiren, by controlling Ang II production, can also inhibit vasoconstriction but additionally shifts water and sodium balance toward levels necessary for normotensive conditions. The combined action of aliskiren and amlodipine on these two central blood pressure-regulating factors (vasoconstriction and RAAS-mediated hypertensive effects) results in more effective antihypertensive effects than seen with monotherapy.

Rasilamlo was studied in a number of active and placebo-controlled trials and long-term trials which included a total of 5,570 hypertensive patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

In hypertensive patients not controlled by the component monotherapies, once-daily administration of Rasilamlo provided dose-dependent clinically meaningful reductions in both systolic and diastolic blood pressure.

When given to patients whose blood pressure was not adequately controlled by either aliskiren or amlodipine, Rasilamlo results in greater blood pressure reductions after one week of treatment than the component monotherapies and a near-maximal effect is achieved after four weeks of therapy.

In a study in 820 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/amlodipine 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 18.0/13.1 mmHg, which were statistically significantly greater than aliskiren 300 mg monotherapy. The combination at a dose of 300 mg/5 mg also showed statistically significantly greater blood pressure reduction than aliskiren 300 mg monotherapy. In a subset of 584 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 7.9/4.8 mmHg and 11.7/7.7 mmHg for the 300/5 mg and 300/10 mg strengths respectively compared to aliskiren 300 mg (the subset constitutes patients without aberrant readings, defined as difference in systolic blood pressure (SBP) ≥10 mmHg at baseline or endpoint).

In a study in 847 randomised patients not adequately responsive to amlodipine 10 mg treatment, the combination of aliskiren/amlodipine 150 mg/10 mg and 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 11.0/9.0 mmHg and 14.4/11.0 mmHg respectively, which were statistically greater than for amlodipine 10 mg monotherapy. In a subset of 549 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 4.0/2.2 mmHg and 7.6/4.7 mmHg for the 150/10 mg and 300/10 mg strengths respectively compared to amlodipine 10 mg (the subset constitutes patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

In a study in 545 randomised patients not adequately responsive to 5 mg amlodipine, the combination of aliskiren 150 mg/amlodipine 5 mg resulted in greater blood pressure reduction than those patients remaining on amlodipine 5 mg.

In an 8-week randomised, double-blind, placebo-controlled, parallel group factorial study in 1,688 randomised patients with mild to moderate hypertension, treatment with Rasilamlo at doses from 150 mg/5 mg to 300 mg/10 mg produced dose-dependent clinically meaningful mean blood pressure reductions (systolic/diastolic) ranging between 20.6/14.0 mmHg and 23.9/16.5 mmHg, respectively, compared to 15.4/10.2 mmHg for aliskiren 300 mg, 21.0/13.8 mmHg for amlodipine 10 mg and 6.8/5.4 mmHg with placebo in a population of patients with mean baseline blood pressure of 157.3/99.7 mmHg. These were statistically significant versus placebo and aliskiren for all doses. The blood pressure reductions with the combination were maintained throughout the entire 24-hour dose interval. In a subset of 1,069 patients, Rasilamlo produced mean blood pressure reductions (systolic/diastolic) ranging between 20.6/13.6 mmHg and 24.2/17.3 mmHg (the subset of patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

The safety of Rasilamlo has been evaluated in studies of up to one year duration.

The effects of Rasilamlo on all cause and cardiovascular mortality and on cardiovascular morbidity and target organ damage are currently unknown.

Rasilamlo has been administered to more than 2,800 patients in completed clinical trials, including 372 patients for one year or more. Treatment with Rasilamlo at doses up to 300 mg/10 mg had an overall incidence of adverse experiences similar to the component monotherapies. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. There were no new adverse reactions which occurred specifically with Rasilamlo in addition to those known to be associated with the individual monotherapies. In a double-blind, randomised placebo-controlled study in 1,688 patients with mild or moderate hypertension, discontinuation of therapy due to a clinical adverse event occurred in 1.7% of patients treated with Rasilamlo versus 1.5% of patients given placebo.

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

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

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

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

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

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

In 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.

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

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

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

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

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. 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.

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

No long-term efficacy data for aliskiren in patients with heart failure are currently available.

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasilamlo 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 $_{0\text{-}tau}$ by 67% in hypertensive patients. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

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 (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

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

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients aged 6 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).

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 "Transporters" above and sections 4.2, 4.4 and 5.3).

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

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

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

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

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

Aliskiren/amlodipine

Following oral administration of Rasilamlo, the median peak plasma concentration time is within 3 hours for aliskiren and 8 hours for amlodipine. The rate and extent of absorption of Rasilamlo are similar in fasting state to those of aliskiren and amlodipine when administered as individual monotherapies. A bioequivalence study under light meal conditions has not been conducted for Rasilamlo.

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

Characteristics in patients

Aliskiren

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

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.

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 aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2).

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

The pharmacokinetics of 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.

Amlodipine

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

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

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

5.3 Preclinical safety data

Aliskiren

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

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

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

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

Juvenile Animal Studies

A repeat-dose toxicity study was conducted in juvenile rats 8 days post-partum for 4 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. High acute mortality (within hours) and severe morbidity were observed at 100 and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose (MRHD) on mg/m^2 basis assuming a 60 kg adult patient) with no cause of death established and occurring without signs or prodromal symptoms. The ratio of lethal dose of 100 mg/kg/day and no-observed-adverse-effect-level (NOAEL) of 30 mg/kg/day is unexpectedly low.

Another repeat-dose toxicity study was conducted in juvenile rats 14 days post-partum for 8 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. Delayed mortality was observed at 300 mg/kg/day (8.5-fold the MRHD on mg/m2 basis assuming a 60 kg adult patient) with no cause of death established.

For the surviving juvenile rats, no effects on behavioural or reproductive performance were observed.

Plasma aliskiren exposure (AUC) in rats aged 8 days was nearly 4-fold higher than that in rats aged 14 days at 100 mg/kg/day. Plasma aliskiren exposure in rats aged 14 days was between 85- and 387-fold higher than that in adult rats aged 64 days.

A single dose study was conducted in juvenile rats aged 14, 21, 24, 28, 31 or 36 days post-partum. No mortality or significant toxicity was observed. The plasma exposure was approximately 100-fold higher in rats aged 14 days and 3-fold higher in rats aged 21 days compared to adult rats.

A mechanistic study was conducted to investigate the relationship between age, aliskiren exposure and MDR1 and OATP2 expression maturation in rats. The results showed that developmental changes of aliskiren exposure correlated with the ontogeny of transporter maturation in jejunum, liver, kidney and brain.

The pharmacokinetics of aliskiren was evaluated in rats aged from 8 to 28 days after intravenous administration of aliskiren 3 mg/kg. The clearance of aliskiren increased in an age-dependent manner. Clearance in rats aged 8 or 14 days was similar, but at these ages the clearance was only about 23% of clearance in rats aged 21 days and 16% of clearance in rats aged 28 days.

These studies indicate that excessive aliskiren exposure (>400-fold higher in 8-day old rats compared with adult rats) and high acute toxicity in juvenile rats are caused by immature MDR1, which suggests that in paediatric patients with immature MDR1, there is a potential for aliskiren overexposure (see sections 4.2, 4.3 and 5.2).

Amlodipine

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

Reproductive toxicology

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

Impairment of fertility

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

Carcinogenesis, mutagenesis

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

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

*Based on patient weight of 50 kg

Rasilamlo

Preclinical safety studies have demonstrated that the combination of aliskiren and amlodipine was well tolerated in rats. The findings from the 2- and 13-week oral toxicity studies in rats were consistent with those of aliskiren and amlodipine when both active substances are administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PCTFE – Alu blisters:
18 months

PA/Alu/PVC – Alu blisters:
18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets
Multi-packs containing 280 tablets (20 packs of 14)

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

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multi-packs containing 98 tablets (2 packs of 49) and 280 tablets (20 packs of 14)

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/029-042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Brown-yellow, convex, ovaloid tablet with a bevelled edge, with "T12" debossed on one side and "NVR" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rasilamlo is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled with aliskiren or amlodipine used alone.

4.2 Posology and method of administration

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

The antihypertensive effect is manifested within 1 week and the effect is near maximal at around 4 weeks. If blood pressure remains uncontrolled after 4 to 6 weeks of therapy, the dose may be titrated up to a maximum of 300 mg aliskiren/10 mg amlodipine. Dose should be individualised and adjusted according to the patient's clinical response.

Rasilamlo may be administered with other antihypertensive medicinal products 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).

Posology in patients not adequately controlled with aliskiren or amlodipine monotherapy
Rasilamlo 300 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled with aliskiren 300 mg or amlodipine 10 mg alone or Rasilamlo 150 mg/10 mg or Rasilamlo 300 mg/5 mg.

A patient who experiences dose limiting adverse reactions on either component alone may be switched to Rasilamlo containing a lower dose of that component to achieve similar blood pressure reductions.

Individual dose titration with each of the two components may be recommended before changing to the fixed combination. When clinically appropriate and in line with the above-mentioned posology, direct change from monotherapy to the fixed combination may be considered.

Special populations

Renal impairment

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (GFR 89-60 ml/min/1.73 m^2 and 59-30 ml/min/1.73 m^2, respectively, see sections 4.4 and 5.2). Rasilamlo is not recommended in patients with severe renal impairment (GFR <30 ml/min/1.73 m^2).

Hepatic impairment

Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment; therefore, caution should be exercised when administering Rasilamlo to patients with hepatic impairment.

Elderly people (over 65 years)

There is limited experience with Rasilamlo, in particular in patients aged 75 years or older. Therefore, particular caution should be exercised in these patients. 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 Rasilamlo in children below age 18 have not been established. No data are available.

Rasilamlo 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 because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilamlo should be taken with a light meal once a day, preferably at the same time each day. 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 other dihydropyridine derivatives.
- 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 Rasilamlo with an ACEI or an 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).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- 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, Rasilamlo therapy should be stopped (see section 4.8).

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and 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
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

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

Risk of symptomatic hypotension
Symptomatic hypotension could occur after initiation of treatment with Rasilamloin 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 Rasilamlo, or the treatment should start under close medical supervision. In patients with uncomplicated hypertension treated with Rasilamlo in short-term controlled trials, the incidence of hypotension was low (0.2%).

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. Rasilamlo 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-aldosterone system, caution should be exercised when Rasilamlo 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.

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.

Hepatic impairment
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Caution should be exercised when administering Rasilamlo to patients with hepatic impairment (see sections 4.2 and 5.2).

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

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

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

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

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

Special caution is necessary in patients with a hypersensitivity predisposition.

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

If anaphylactic reactions or angioedema occur, Rasilamlo 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, Rasilamlo 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.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Information on Rasilamlo interactions
No interaction studies with other medicinal products were performed with Rasilamlo. Therefore, information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

Co-administration of aliskiren and amlodipine does not cause meaningful changes in the steady-state pharmacokinetic exposure (AUC) and the maximum concentration (C_{max}) of either component in healthy volunteers.

Information on aliskiren interactions
Contraindicated (see section 4.3)
- *P-gp potent inhibitors*

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

Not recommended (see section 4.2)
- *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 Rasilamlo. 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 Rasilamlo.

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 trials. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

- *Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-medication with an agent affecting the level of serum potassium is considered necessary, caution is advisable.

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

As with other medicinal products acting on the renin-angiotensin-aldosterone system, 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 interaction with organic anion transporting polypeptide (OATP) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

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

- *Warfarin*

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

- *Food interactions*

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

No interactions

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

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

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

- *CYP450 interactions*

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

- *P-gp substrates or weak inhibitors*

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

- *Organic anion transporting polypeptide (OATP) inhibitors*

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

Information on amlodipine interactions

Effects of other medicinal products on amlodipine

Caution required with concomitant use

- *CYP3A4 inhibitors*

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

- *CYP3A4 inducers*

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

- *Grapefruit juice*

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

- *Dantrolene (infusion)*

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

Effects of amlodipine on other medicinal products

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

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

No interactions

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception in males and females

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

Pregnancy

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

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

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

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

Breast-feeding
It is unknown whether aliskiren and/or amlodipine are excreted in human milk. Aliskiren was secreted in the milk of lactating rats.

Since there is insufficient/limited information on the excretion of aliskiren and amlodipine in human or animal breast milk, a risk to the newborns/infants cannot be excluded. It is therefore not recommended for women who are breast-feeding to use Rasilamlo.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rasilamlo therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

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

4.7 Effects on 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 Rasilamlo.

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Rasilamlo presented below is based on clinical studies performed with Rasilamlo and the known safety profile of the individual components aliskiren and amlodipine. Safety information for Rasilamlo in patients aged 75 years and older is limited.

The most frequent adverse reactions for Rasilamlo are hypotension and peripheral oedema. The adverse reactions previously reported with one of the individual components of Rasilamlo (aliskiren and amlodipine) and included in the tabulated list of adverse reactions may occur with Rasilamlo.

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

Blood and lymphatic system disorders	
Very rare	Leukopenia[am], thrombocytopenia[am]
Immune system disorders	
Rare	Anaphylactic reactions[a], hypersensitivity reactions[a]
Very rare	Allergic reactions[am]
Metabolism and nutrition disorders	
Very rare	Hyperglycaemia[am]
Psychiatric disorders	
Uncommon	Insomnia[am], mood changes (including anxiety)[am], depression[am]
Rare	Confusion[am]
Nervous system disorders	
Common	Somnolence[am], headache (especially at the beginning of treatment)[am]
Uncommon	Tremor[am], dysgeusia[am], syncope[am], hypoesthesia[am], paraesthesia[am]
Very rare	Hypertonia[am], peripheral neuropathy[am]
Eye disorders	
Uncommon	Visual disturbance (including diplopia)[am]
Ear and labyrinth disorders	
Uncommon	Tinnitus[am]
Not known	Vertigo[a]
Cardiac disorders	
Common	Dizziness[a,am], palpitations[a,am], peripheral oedema[c,a,am]*
Very rare	Myocardial infarction[am], arrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation)[am]
Vascular disorders	
Common	Flushing[am], hypotension[c,a,am]
Very rare	Vasculitis[am]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea[a, am], rhinitis[am], cough[a,am]
Gastrointestinal disorders	
Common	Diarrhoea[a], abdominal pain[am], nausea[a,am]
Uncommon	Vomiting[a,am], dyspepsia[am], altered bowel habits (including diarrhoea and constipation)[am], dry mouth[am]
Very rare	Pancreatitis[am], gastritis[am], gingival hyperplasia[am]
Hepatobiliary disorders	
Very rare	Hepatitis[a,am], jaundice[a,am], hepatic enzymes increased (mostly consistent with cholestasis)[am]
Not known	Liver disorder[a,]**, liver failure[a,]***

Skin and subcutaneous tissue disorders	
Uncommon	Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome[a], toxic epidermal necrolysis (TEN)[a], oral mucosal reactions[a], rash[a,am], pruritus[a,am], urticaria[a,am], alopecia[am], purpura[am], skin decolouration[am], hyperhidrosis[am], exanthema[am]
Rare	Angioedema[a], erythema[a]
Very rare	Erythema multiforme[am], exfoliative dermatitis[am], Stevens-Johnson syndrome[am], Quincke oedema[am], photosensitivity[am]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia[a,am], ankle swelling[am]
Uncommon	Myalgia[am], muscle cramps[am], back pain[am]
Renal and urinary disorders	
Uncommon	Acute renal failure[a], renal impairment[a], micturition disorder[am], nocturia[am], increased urinary frequency[am]
Reproductive system and breast disorders	
Uncommon	Impotence[am], gynaecomastia[am]
General disorders and administration site conditions	
Common	Fatigue[am]
Uncommon	Chest pain[am], asthenia[am], pain[am], malaise[am]
Investigations	
Common	Hyperkalaemia[a]
Uncommon	Liver enzyme increased[a], weight increase[am], weight decrease[am]
Rare	Haemoglobin decreased[a], haematocrit decreased[a], blood creatinine increased[a]
Not known	Hyponatraemia[a]

[c] Adverse reaction observed with Rasilamlo;
[a] Adverse reaction observed with monotherapy with aliskiren;
[am] Adverse reaction observed with monotherapy with amlodipine;
* Peripheral oedema is a known, dose-dependent adverse reaction of amlodipine and has also been reported with aliskiren therapy in post-marketing experience. The most frequently reported adverse reaction for Rasilamlo in clinical trials was peripheral oedema, which occurred at a frequency lower than or equal to that of the corresponding amlodipine doses, but higher than with aliskiren;
** 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.

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

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

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

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

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

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

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

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

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

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

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

Serum potassium: Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

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

Amlodipine
Exceptional cases of extrapyramidal syndrome have been reported.

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
There is no experience of overdose with Rasilamlo. The most likely manifestation of overdose for Rasilamlo would be hypotension, related to the antihypertensive effect of aliskiren and amlodipine.

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

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

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, renin inhibitors, ATC code: C09XA53

Rasilamlo combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: aliskiren belongs to the class of direct renin inhibitors and amlodipine belongs to the calcium antagonist class.

Rasilamlo

The use of combined treatment with aliskiren and amlodipine arises from the actions of these two medicinal products on different but complementary systems that regulate blood pressure. Calcium channel blockers act to prevent the influx of calcium into the vascular smooth muscle cells in the vessel wall, thereby preventing smooth muscle cell contraction and vasoconstriction. Renin inhibitors suppress the enzymatic activity of renin, and thereby block the formation of Angiotensin II, the major effector molecule of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II causes vasoconstriction and sodium and water reabsorption. Thus, amlodipine directly inhibits vasoconstriction and reduces vascular resistance, while aliskiren, by controlling Ang II production, can also inhibit vasoconstriction but additionally shifts water and sodium balance toward levels necessary for normotensive conditions. The combined action of aliskiren and amlodipine on these two central blood pressure-regulating factors (vasoconstriction and RAAS-mediated hypertensive effects) results in more effective antihypertensive effects than seen with monotherapy.

Rasilamlo was studied in a number of active and placebo-controlled trials and long-term trials which included a total of 5,570 hypertensive patients with mild to moderate hypertension (diastolic blood pressure between 90 mmHg and 109 mmHg).

In hypertensive patients not controlled by the component monotherapies, once-daily administration of Rasilamlo provided dose-dependent clinically meaningful reductions in both systolic and diastolic blood pressure.

When given to patients whose blood pressure was not adequately controlled by either aliskiren or amlodipine, Rasilamlo results in greater blood pressure reductions after one week of treatment than the component monotherapies and a near-maximal effect is achieved after four weeks of therapy.

In a study in 820 randomised patients not adequately responsive to aliskiren 300 mg treatment, the combination of aliskiren/amlodipine 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 18.0/13.1 mmHg, which were statistically significantly greater than aliskiren 300 mg monotherapy. The combination at a dose of 300 mg/5 mg also showed statistically significantly greater blood pressure reduction than aliskiren 300 mg monotherapy. In a subset of 584 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 7.9/4.8 mmHg and 11.7/7.7 mmHg for the 300/5 mg and 300/10 mg strengths respectively compared to aliskiren 300 mg (the subset constitutes patients without aberrant readings, defined as difference in systolic blood pressure (SBP) ≥10 mmHg at baseline or endpoint).

In a study in 847 randomised patients not adequately responsive to amlodipine 10 mg treatment, the combination of aliskiren/amlodipine 150 mg/10 mg and 300 mg/10 mg produced systolic/diastolic mean blood pressure reductions of 11.0/9.0 mmHg and 14.4/11.0 mmHg respectively, which were statistically greater than for amlodipine 10 mg monotherapy. In a subset of 549 patients, the combination of aliskiren/amlodipine produced additional systolic/diastolic mean blood pressure reductions of 4.0/2.2 mmHg and 7.6/4.7 mmHg for the 150/10 mg and 300/10 mg strengths respectively compared to amlodipine 10 mg (the subset constitutes patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

In a study in 545 randomised patients not adequately responsive to 5 mg amlodipine, the combination of aliskiren 150 mg/amlodipine 5 mg resulted in greater blood pressure reduction than those patients remaining on amlodipine 5 mg.

In an 8-week randomised, double-blind, placebo-controlled, parallel group factorial study in 1,688 randomised patients with mild to moderate hypertension, treatment with Rasilamlo at doses from 150 mg/5 mg to 300 mg/10 mg produced dose-dependent clinically meaningful mean blood pressure reductions (systolic/diastolic) ranging between 20.6/14.0 mmHg and 23.9/16.5 mmHg, respectively, compared to 15.4/10.2 mmHg for aliskiren 300 mg, 21.0/13.8 mmHg for amlodipine 10 mg and 6.8/5.4 mmHg with placebo in a population of patients with mean baseline blood pressure of 157.3/99.7 mmHg. These were statistically significant versus placebo and aliskiren for all doses. The blood pressure reductions with the combination were maintained throughout the entire 24-hour dose interval. In a subset of 1,069 patients, Rasilamlo produced mean blood pressure reductions (systolic/diastolic) ranging between 20.6/13.6 mmHg and 24.2/17.3 mmHg (the subset of patients without aberrant readings, defined as difference in SBP ≥10 mmHg at baseline or endpoint).

The safety of Rasilamlo has been evaluated in studies of up to one year duration.

The effects of Rasilamlo on all cause and cardiovascular mortality and on cardiovascular morbidity and target organ damage are currently unknown.

Rasilamlo has been administered to more than 2,800 patients in completed clinical trials, including 372 patients for one year or more. Treatment with Rasilamlo at doses up to 300 mg/10 mg had an overall incidence of adverse experiences similar to the component monotherapies. The incidence of adverse events did not show any association with gender, age, body mass index, race or ethnicity. There were no new adverse reactions which occurred specifically with Rasilamlo in addition to those known to be associated with the individual monotherapies. In a double-blind, randomised placebo-controlled study in 1,688 patients with mild or moderate hypertension, discontinuation of therapy due to a clinical adverse event occurred in 1.7% of patients treated with Rasilamlo versus 1.5% of patients given placebo.

Aliskiren

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

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

Hypertension

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

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

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

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

In 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.

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

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

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

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

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. 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.

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

No long-term efficacy data for aliskiren in patients with heart failure are currently available.

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

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

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

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

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

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

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

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

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

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

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

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

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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rasilamlo 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 $_{0\text{-}tau}$ by 67% in hypertensive patients. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

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 (78%). Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4. Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, mean plasma clearance is approximately 9 l/h.

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

Paediatric population
In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients aged 6 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).

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 "Transporters" above and sections 4.2, 4.4 and 5.3).

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

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

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

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

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

Aliskiren/amlodipine

Following oral administration of Rasilamlo, the median peak plasma concentration time is within 3 hours for aliskiren and 8 hours for amlodipine. The rate and extent of absorption of Rasilamlo are similar in fasting state to those of aliskiren and amlodipine when administered as individual monotherapies. A bioequivalence study under light meal conditions has not been conducted for Rasilamlo.

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

Characteristics in patients

Aliskiren

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

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.

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 aliskiren is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). Aliskiren is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2).

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

The pharmacokinetics of 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.

Amlodipine

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

A population pharmacokinetic study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

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

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

5.3 Preclinical safety data

Aliskiren

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

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

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

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

Juvenile Animal Studies

A repeat-dose toxicity study was conducted in juvenile rats 8 days post-partum for 4 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. High acute mortality (within hours) and severe morbidity were observed at 100 and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose (MRHD) on mg/m^2 basis assuming a 60 kg adult patient) with no cause of death established and occurring without signs or prodromal symptoms. The ratio of lethal dose of 100 mg/kg/day and no-observed-adverse-effect-level (NOAEL) of 30 mg/kg/day is unexpectedly low.

Another repeat-dose toxicity study was conducted in juvenile rats 14 days post-partum for 8 weeks with aliskiren dosing at 30, 100 or 300 mg/kg/day. Delayed mortality was observed at 300 mg/kg/day (8.5-fold the MRHD on mg/m2 basis assuming a 60 kg adult patient) with no cause of death established.

For the surviving juvenile rats, no effects on behavioural or reproductive performance were observed.

Plasma aliskiren exposure (AUC) in rats aged 8 days was nearly 4-fold higher than that in rats aged 14 days at 100 mg/kg/day. Plasma aliskiren exposure in rats aged 14 days was between 85- and 387-fold higher than that in adult rats aged 64 days.

A single dose study was conducted in juvenile rats aged 14, 21, 24, 28, 31 or 36 days post-partum. No mortality or significant toxicity was observed. The plasma exposure was approximately 100-fold higher in rats aged 14 days and 3-fold higher in rats aged 21 days compared to adult rats.

A mechanistic study was conducted to investigate the relationship between age, aliskiren exposure and MDR1 and OATP2 expression maturation in rats. The results showed that developmental changes of aliskiren exposure correlated with the ontogeny of transporter maturation in jejunum, liver, kidney and brain.

The pharmacokinetics of aliskiren was evaluated in rats aged from 8 to 28 days after intravenous administration of aliskiren 3 mg/kg. The clearance of aliskiren increased in an age-dependent manner. Clearance in rats aged 8 or 14 days was similar, but at these ages the clearance was only about 23% of clearance in rats aged 21 days and 16% of clearance in rats aged 28 days.

These studies indicate that excessive aliskiren exposure (>400-fold higher in 8-day old rats compared with adult rats) and high acute toxicity in juvenile rats are caused by immature MDR1, which suggests that in paediatric patients with immature MDR1, there is a potential for aliskiren overexposure (see sections 4.2, 4.3 and 5.2).

Amlodipine

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

Reproductive toxicology

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

Impairment of fertility

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

Carcinogenesis, mutagenesis

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

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

*Based on patient weight of 50 kg

Rasilamlo

Preclinical safety studies have demonstrated that the combination of aliskiren and amlodipine was well tolerated in rats. The findings from the 2- and 13-week oral toxicity studies in rats were consistent with those of aliskiren and amlodipine when both active substances are administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous

Coating
Hypromellose
Macrogol
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PCTFE – Alu blisters:
18 months

PA/Alu/PVC – Alu blisters:
18 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) - Alu calendar blisters:
Single pack containing 14, 28, 56, 98 tablets
Multi-packs containing 280 tablets (20 packs of 14)

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

PA/Alu/PVC – Alu calendar blisters:
Single pack containing 14, 28, 56 tablets
Multi-packs containing 98 tablets (2 packs of 49) and 280 tablets (20 packs of 14)

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

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/043-056

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
56x1 tablet
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/001	14 tablets (PVC/PCTFE blisters)
EU/1/11/686/010	14 tablets (PA/Alu/PVC blisters)
EU/1/11/686/002	28 tablets (PVC/PCTFE blisters)
EU/1/11/686/011	28 tablets (PA/Alu/PVC blisters)
EU/1/11/686/003	30 tablets (PVC/PCTFE blisters)
EU/1/11/686/004	56 tablets (PVC/PCTFE blisters)
EU/1/11/686/012	56 tablets (PA/Alu/PVC blisters)
EU/1/11/686/007	56x1 tablet (PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/005	90 tablets (PVC/PCTFE blisters)
EU/1/11/686/006	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.
Component of a multipack comprising 20 packs, each containing 14 tablets.
Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/013	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/008	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/009	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/014	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 280 (20 packs of 14) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/013	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/008	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/009	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/014	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)
CALENDAR BLISTERS ONLY

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (PCTFE)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/5 mg tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
56x1 tablet
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/015	14 tablets (PVC/PCTFE blisters)
EU/1/11/686/024	14 tablets (PA/Alu/PVC blisters)
EU/1/11/686/016	28 tablets (PVC/PCTFE blisters)
EU/1/11/686/025	28 tablets (PA/Alu/PVC blisters)
EU/1/11/686/017	30 tablets (PVC/PCTFE blisters)
EU/1/11/686/018	56 tablets (PVC/PCTFE blisters)
EU/1/11/686/026	56 tablets (PA/Alu/PVC blisters)
EU/1/11/686/021	56x1 tablet (PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/019	90 tablets (PVC/PCTFE blisters)
EU/1/11/686/020	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.
Component of a multipack comprising 20 packs, each containing 14 tablets.
Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/027	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/022	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/023	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/028	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 280 (20 packs of 14) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/027	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/022	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/023	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/028	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 150 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)
CALENDAR BLISTERS ONLY

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (PCTFE)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 150 mg/10 mg tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
56x1 tablet
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/029	14 tablets (PVC/PCTFE blisters)
EU/1/11/686/038	14 tablets (PA/Alu/PVC blisters)
EU/1/11/686/030	28 tablets (PVC/PCTFE blisters)
EU/1/11/686/039	28 tablets (PA/Alu/PVC blisters)
EU/1/11/686/031	30 tablets (PVC/PCTFE blisters)
EU/1/11/686/032	56 tablets (PVC/PCTFE blisters)
EU/1/11/686/040	56 tablets (PA/Alu/PVC blisters)
EU/1/11/686/035	56x1 tablet (PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/033	90 tablets (PVC/PCTFE blisters)
EU/1/11/686/034	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.
Component of a multipack comprising 20 packs, each containing 14 tablets.
Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/041	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/036	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/037	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/042	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 5 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 280 (20 packs of 14) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/041	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/036	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/037	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/042	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)
CALENDAR BLISTERS ONLY

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg film-coated tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (PCTFE)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/5 mg tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF SINGLE PACK/CARTON OF UNIT PACK (perforated unit dose blister)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

14 tablets
28 tablets
30 tablets
56 tablets
56x1 tablet
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/043	14 tablets (PVC/PCTFE blisters)
EU/1/11/686/052	14 tablets (PA/Alu/PVC blisters)
EU/1/11/686/044	28 tablets (PVC/PCTFE blisters)
EU/1/11/686/053	28 tablets (PA/Alu/PVC blisters)
EU/1/11/686/045	30 tablets (PVC/PCTFE blisters)
EU/1/11/686/046	56 tablets (PVC/PCTFE blisters)
EU/1/11/686/054	56 tablets (PA/Alu/PVC blisters)
EU/1/11/686/049	56x1 tablet (PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/047	90 tablets (PVC/PCTFE blisters)
EU/1/11/686/048	98 tablets (PVC/PCTFE blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Component of a multipack comprising 2 packs, each containing 49 tablets.
Component of a multipack comprising 2 packs, each containing 49x1 tablet.
Component of a multipack comprising 20 packs, each containing 14 tablets.
Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/055	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/050	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/051	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/056	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg aliskiren (as aliskiren hemifumarate) and 10 mg amlodipine (as amlodipine besylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack containing 98 (2 packs of 49) tablets.
Multipack containing 280 (20 packs of 14) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/686/055	98 tablets (2x49, PA/Alu/PVC blisters)
EU/1/11/686/050	98 tablets (2x49x1, PVC/PCTFE single-unit-dose blisters)
EU/1/11/686/051	280 tablets (20x14, PVC/PCTFE blisters)
EU/1/11/686/056	280 tablets (20x14, PA/Alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rasilamlo 300 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PVC/PCTFE OR PA/Alu/PVC)
CALENDAR BLISTERS ONLY

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg film-coated tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (PCTFE)

1. NAME OF THE MEDICINAL PRODUCT

Rasilamlo 300 mg/10 mg tablets
Aliskiren/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Rasilamlo 150 mg/5 mg film-coated tablets
Rasilamlo 150 mg/10 mg film-coated tablets
Rasilamlo 300 mg/5 mg film-coated tablets
Rasilamlo 300 mg/10 mg film-coated tablets
Aliskiren/amlodipine

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 Rasilamlo is and what it is used for

What Rasilamlo is
Rasilamlo contains two active substances, called aliskiren and amlodipine. Both of these 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 raises blood pressure. Lowering the amount of angiotensin II allows the blood vessels to relax; this lowers blood pressure.

Amlodipine belongs to a group of medicines known as calcium channel blockers, which help to control high blood pressure. Amlodipine causes blood vessels to dilate and relax, thus blood pressure is lowered.

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 Rasilamlo is used for
Rasilamlo is used to treat high blood pressure in adult patients whose blood pressure is not sufficiently controlled with aliskiren or amlodipine alone.

2. What you need to know before you take Rasilamlo

Do not take Rasilamlo
- if you are allergic to aliskiren or amlodipine, to any of the other ingredients of this medicine (listed in section 6) or to other dihydropyridine-derived medicines (known as calcium channel blockers)
- 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 between three and nine months pregnant
- if you are taking any of the following medicines
  - ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis)
  - itraconazole (a medicine used to treat fungal infections)
  - quinidine (a medicine used to correct heart rhythm)
- if you have diabetes 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 you have very low blood pressure
- if you are suffering from shock, including cardiogenic shock
- if you have a narrowing of the aortic heart valve (aortic stenosis)
- if you have heart failure after an acute heart attack

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

Warnings and precautions
Talk to your doctor before taking Rasilamlo:
- if you are suffering from vomiting or diarrhoea or if you are taking a diuretic (a medicine to increase the amount of urine you produce)
- if you have already experienced angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking Rasilamlo and contact your doctor
- 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 diabetes (high blood sugar)
- if you suffer from heart problems
- if you are on a low-salt diet
- if your urine flow has decreased markedly for 24 hours or more and/or if you have serious kidney problems (e.g. require dialysis) or a narrowing or blockage of the arteries that supply blood to your kidney
- if you have impaired kidney function, your doctor will carefully consider whether Rasilamlo is suitable for you and may wish to monitor you carefully
- if you suffer from liver problems (impaired liver function)

- if you have renal artery stenosis (narrowing of the blood vessels to one of 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 information under the heading "Do not take Rasilamlo".

Children and adolescents
Rasilamlo is for use in adults.
Rasilamlo must not be used in children 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.

Elderly people
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 Rasilamlo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are using the following medicines:
- an angiotensin II receptor blocker or an angiotensin converting enzyme inhibitor (see also information under the headings "Do not take Rasilamlo" and "Warnings and precautions")
- medicines used to lower blood pressure, diuretics (medicines to increase the amount of urine you produce), especially potassium-sparing medicines, potassium supplements, potassium-containing salt substitutes, or heparin
- 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
- clarithromycin, telithromycin, erythromycin which are antibiotics used to treat infections
- amiodarone, a medicine used to treat abnormal heart rhythms
- atorvastatin, a medicine used to treat high cholesterol
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling)
- antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone)
- rifampicin, a medicine used to prevent or treat infections
- St. John's wort (hypericum perforatum), a herbal medicine used to elevate mood
- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs) (used especially in patients over 65 years old)
- diltiazem, a medicine used to treat heart problems
- ritonavir, a medicine used to treat viral infection

Your doctor may need to change your dose and/or take other precautions if you are taking one of the following medicines:
- furosemide or torasemide, medicines belonging to the type known as diuretics, which are used to increase the amount of urine you produce and are also used to treat a certain kind of heart problem (heart failure) or oedema (swelling)
- some medicines used to treat infections, such as ketoconazole

Rasilamlo with food and drink
You should avoid taking this medicine together with fruit juice and/or drinks containing plant extracts (including herbal teas).

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

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Rasilamlo is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Amlodipine, one of the active substances in Rasilamlo, may make you feel dizzy and drowsy. If you experience this symptom, do not drive or use tools or machines.

3. How to take Rasilamlo

Always take this medicine exactly as your doctor has told you and do not exceed the recommended dose. Check with your doctor or pharmacist if you are not sure.

The usual dose of Rasilamlo is one tablet a day.
The effect on blood pressure is seen within 1 week and maximum effect is reached at around 4 weeks. If your blood pressure is not controlled after 4 to 6 weeks, your doctor may adjust your dose.

Method of administration
Swallow the tablet whole with some water. You should take this medicine with a light meal once a day, preferably at the same time each day. You should 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 Rasilamlo than you should
If you have accidentally taken too many Rasilamlo tablets, talk to a doctor immediately. You may require medical attention.

If you forget to take Rasilamlo
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.

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.

Fainting and/or light-headedness linked to low blood pressure could occur at the beginning of treatment with Rasilamlo. If you experience these, tell your doctor **immediately**.

As for any combination of two active substances, side effects associated with each individual component cannot be excluded. The adverse reactions previously reported with one or both of the two active substances (aliskiren and amlodipine) of Rasilamlo and listed below may occur with Rasilamlo.

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 skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions - red skin, blistering of the lips, eyes or mouth, skin peeling, fever) *(uncommon: may affect up to 1 in 100 people)*.
- Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness *(rare: may affect up to 1 in 1,000 people)*.
- Nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes (may be signs of liver disorder) *(frequency not known)*.

Other side effects may include:

Common (may affect up to 1 in 10 people):

- low blood pressure
- swelling, including swelling of hands, ankles or feet (peripheral oedema)
- diarrhoea
- joint pain (arthralgia)
- high level of potassium in the blood
- dizziness
- sleepiness
- headache
- hot flushes
- abdominal pain
- nausea
- tiredness
- palpitations (awareness of your heart beat)

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)
- severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions - red skin, blistering of the lips, eyes or mouth, skin peeling, fever)
- cough
- itching
- rash (including itchy rash and urticaria)
- increased liver enzymes
- insomnia
- mood changes (including anxiety)
- depression
- trembling

- disturbed sense of taste
- sudden, temporary loss of consciousness
- decreased skin sensitivity
- tingling or numbness
- vision disorder (including double vision)
- ringing noise in ears
- shortness of breath
- runny nose
- vomiting
- stomach discomfort after meal
- altered bowel habits (including diarrhoea and constipation)
- dry mouth
- hair loss
- purple skin patches
- skin discolouration
- excessive sweating
- generalised rash
- muscle pain
- muscle cramps
- back pain
- urination disorders
- urination at night
- frequent urination
- impotence
- breast enlargement in men
- chest pain
- weakness
- pain
- feeling unwell
- weight increase
- weight decrease

Rare (may affect up to 1 in 1,000 people):
- 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)
- increased level of creatinine in the blood
- red skin (erythema)
- confusion

Very rare (may affect up to 1 in 10,000 people):
- low level of white blood cells and blood platelets
- high level of sugar in the blood
- increased muscle stiffness and inability to stretch
- sensation of numbness or tingling with sensation of burning in fingers and toes
- heart attack
- irregular heart beat
- inflammation of blood vessels
- severe upper stomach pain
- inflammation of the gastric lining
- bleeding, tender or enlarged gums
- inflammation of the liver

- abnormal liver function test
- skin reaction with skin reddening and peeling, blistering of lips, eyes or mouth
- dry skin, rash, itchy rash
- skin rash with flaking or peeling
- rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever
- swelling mainly of the face and throat
- increased sensitivity of the skin to sun

Not known (frequency cannot be estimated from the available data):
- dizziness with spinning sensation
- low level of sodium in the blood

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

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 Rasilamlo

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
Do not store above 30°C.
Store in the original package in order to protect from moisture.

6. Contents of the pack and other information

What Rasilamlo contains
- Each Rasilamlo 150 mg/5 mg film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 5 mg amlodipine (as besylate). The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc, yellow iron oxide (E172) and red iron oxide (E172).

- Each Rasilamlo 150 mg/10 mg film-coated tablet contains 150 mg aliskiren (as hemifumarate) and 10 mg amlodipine (as besylate). The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172).

- Each Rasilamlo 300 mg/5 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 5 mg amlodipine (as besylate). The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172).

- Each Rasilamlo 300 mg/10 mg film-coated tablet contains 300 mg aliskiren (as hemifumarate) and 10 mg amlodipine (as besylate). The other ingredients are cellulose microcrystalline, crospovidone, povidone, magnesium stearate, silica colloidal anhydrous, hypromellose, macrogol, talc and yellow iron oxide (E172).

What Rasilamlo looks like and contents of the pack
Rasilamlo 150 mg/5 mg film-coated tablets are light yellow, convex, oval film-coated tablets, with "T2" debossed on one side and "NVR" on the other.

Rasilamlo 150 mg/10 mg film-coated tablets are yellow, convex, oval film-coated tablets, with "T7" debossed on one side and "NVR" on the other.

Rasilamlo 300 mg/5 mg film-coated tablets are dark yellow, convex, oval film-coated tablets, with "T11" debossed on one side and "NVR" on the other.

Rasilamlo 300 mg/10 mg film-coated tablets are brown-yellow, convex, oval film-coated tablets, with "T12" debossed on one side and "NVR" on the other.

Rasilamlo is available in packs containing 14, 28, 56 or 98 tablets (in calendar blisters), 30 or 90 tablets (in normal blisters) and 56x1 tablet (as perforated unit dose blisters).

It is also available in multi-packs of 98 tablets (2 packs of 49) and 280 tablets (20 packs of 14) in calendar blisters and 98x1 tablet (2 packs of 49x1) as perforated unit dose blisters.

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

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for aliskiren / aliskiren, amlodipine / aliskiren, hydrochlorothiazide, the scientific conclusions of CHMP are as follows:

During the reporting a number of serious and non-serious adverse drug reactions (ADRs) from post-marketing data sources regarding "hyponatraemia" raised a concern that led to the submission of a cumulative review from the Marketing Authorisation Holder (MAH). The cumulative review retrieved 187 cases out of which 57 were sufficiently documented, in 8 of these cases a causal relationship could not be ruled out. In 3 additional cases where severe hyponatremia was associated with neurological symptoms such as brain oedema or major confusion and cerebral oedema, causality could also not be excluded.

The MAH submitted an analysis with 1407 cases of "dyspnoea", in 13 of them there was positive dechallenge and three cases with positive rechallenge. The PRAC considered the cases of dechallenge and rechallenge to be important causal relationship information that contributes to confirm the safety signal.

Therefore, in view of available data regarding aliskiren/ aliskiren,amlodipine / aliskiren, hydrochlorothiazide, the PRAC considered that changes to the product information were warranted. The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for aliskiren / aliskiren, amlodipine / aliskiren, hydrochlorothiazide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing aliskiren / aliskiren, amlodipine / aliskiren, hydrochlorothiazide is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.