NOVARTIS

Rasilez®

Composition
Active substance: Aliskiren as aliskiren hemifumarate
Excipients: Tableting excipients

Pharmaceutical form and quantity of active substance per unit
Rasilez® 150 mg
Film-coated tablets containing 150 mg aliskiren

Rasilez® 300 mg
Film-coated tablets containing 300 mg aliskiren

Indications / Potential uses
Treatment of essential hypertension

Dosage and Administration
Rasilez provides effective once daily antihypertensive treatment in adult patients, regardless of sex, age, body mass index or race.
The recommended starting dose of Rasilez is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.
The antihypertensive effect is substantially present, and blood pressure well controlled (85-90%), within two weeks of initiating therapy with 150 mg once daily.
Rasilez may be used alone or in combination with other antihypertensive agents.
Rasilez may be taken with or without food.

Use in elderly patients (over 65 years of age)
No adjustment of the initial dose is required in elderly patients.

Use in patients with renal impairment
No adjustment of the initial dose is required in patients with mild to severe renal impairment, but caution is required in patients with severe renal impairment (see **Warnings and Precautions** and **Pharmacokinetics**).

Use in patients with hepatic impairment
No adjustment of the initial dose is required in patients with mild to severe hepatic impairment (see **Pharmacokinetics**).

Use in children and adolescents
The safety and efficacy of Rasilez have not been investigated in children and adolescents (under 18 years of age). Rasilez is therefore not recommended for use in this patient population.

Contraindications
Hypersensitivity to the active substance or any of the excipients.
Pregnancy and lactation (see **Pregnancy and Lactation**).

Warnings and Precautions
Sodium- or volume-depleted patients
Symptomatic hypotension may occur after initiation of treatment with Rasilez in patients with marked volume depletion and/or massive salt depletion (e.g. those receiving high doses of diuretics). These conditions should therefore be corrected prior to administration of Rasilez. Otherwise, treatment must be initiated under close medical supervision.

Renal impairment
In clinical studies, Rasilez has not been studied in hypertensive patients with severe renal dysfunction (creatinine ≥ 150 µmol/litre for women and ≥ 177 µmol/litre for men and/or estimated GFR < 30 ml/minute), or in patients with a history of dialysis, nephrotic syndrome or renovascular hypertension. When using Rasilez in hypertensive patients with severe renal impairment, caution should be exercised due to the limited clinical availability of safety information for Rasilez in such patients. Other agents that act on the renin-angiotensin system (RAS) may increase serum levels of potassium, creatinine and blood urea nitrogen (BUN) in these patients. A similar effect might also be anticipated with Rasilez.

Renal artery stenosis
No data are available on the use of Rasilez in patients with unilateral or bilateral renal artery stenosis.

Concomitant use of ciclosporin A
Concomitant use of aliskiren with ciclosporin, a highly potent P-glycoprotein inhibitor, is not recommended (see **Interactions**).

Interactions
Rasilez has a low potential for interactions with other medicinal products.
The following compounds have been investigated in clinical pharmacokinetic studies without interactions having been identified: acenocoumarol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, irbesartan, ramipril and hydrochlorothiazide.
Co-administration of aliskiren had no significant impact on the pharmacokinetics of atorvastatin, valsartan, metformin or amlodipine. Therefore, no dose adjustment is necessary when these substances are co-administered. Concomitant administration of aliskiren with the following substances resulted in a 20–30% change in the C_{max} or AUC of aliskiren: valsartan (28% reduction), metformin (28% reduction), amlodipine (29% increase), cimetidine (19% increase).

CYP450 interactions
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A) and does not induce CYP3A4. Aliskiren is only minimally metabolized by the cytochrome P450 enzymes. For this reason, aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce, or are metabolized by these enzymes.

P-glycoprotein interactions
In preclinical studies, MDR1/Mdr1a/1b (Pgp) was found to be the major efflux system involved in the absorption and distribution of aliskiren.

Pgp substrates or weak to moderate inhibitors
No relevant interactions were noted with atenolol or digoxin.

Potent Pgp inhibitors
The steady-state AUC and C_{max} of aliskiren (300 mg) increased by 50% when it was administered with atorvastatin (80 mg). Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that co-administration of aliskiren and ketoconazole enhances gastrointestinal absorption of aliskiren and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of atorvastatin or ketoconazole 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, were well tolerated in controlled clinical studies. Dose adjustment is thus not necessary.

Highly potent Pgp inhibitors
A single-dose drug interaction study in healthy subjects showed that ciclosporin A (200 and 600 mg) increased the C_{max} of 75 mg aliskiren approximately 2.5 times and the AUC approximately 5 times. Concomitant use of the two medicinal products is therefore not recommended (see **Warnings and Precautions**).

Furosemide
When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49%, respectively. Monitoring of efficacy is therefore recommended when initiating therapy, and the dose of furosemide should be adjusted, if necessary, in order to avoid possible underdosage in clinical situations of volume overload.

Potassium and potassium-sparing diuretics
Based on experience with other substances that affect the renin-angiotensin system, serum potassium may rise as a result of concomitant use of aliskiren with potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium. Caution is required if concomitant use is necessary (see **Adverse effects**).

Pregnancy and Lactation
Pregnancy
There are no suitable data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats and rabbits (see **Preclinical data**). Other substances that act directly on the renin-angiotensin system (RAS) have been associated with serious fetal malformations and neonatal death. Like any agent that acts directly on the RAS, Rasilez must therefore not be used during pregnancy or in women planning to become pregnant (see **Contraindications**). Healthcare professionals prescribing any medicinal products that act on the RAS should inform women of childbearing potential about the potential risk of these products during pregnancy. If pregnancy is detected during therapy, Rasilez must be discontinued as soon as possible.

Lactation
Rasilez must not be used by women who are breastfeeding.
It is not known whether aliskiren is excreted in human milk. It was secreted in the milk of lactating rats.

Effects on ability to drive and use machines
There have been no studies of the effects of this product on the ability to drive or use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or fatigue may occasionally occur during the course of any antihypertensive therapy.

Adverse effects
Rasilez has been evaluated for safety in more than 7800 patients, including over 2300 treated for 6 months, and more than 1200 treated for 1 year. The incidence of adverse effects showed no association with sex, age, body mass index, race or dose. Treatment with Rasilez was well tolerated. The overall incidence of side effects following doses up to 300 mg was in the same range as with placebo. Adverse reactions have generally been mild and transient in nature and have only rarely led to discontinuation of therapy. The most common adverse effect was diarrhoea.
In controlled clinical studies, angioedema occurred rarely during treatment with Rasilez. The rate was similar to rates with placebo and hydrochlorothiazide. In the event of any signs suggesting an allergic reaction (in particular difficulties in breathing or swallowing, or swelling of the face, extremities, eyes, lips or tongue), patients should discontinue treatment and contact their physicians.
Rasilez use was not associated with an increased incidence of dry cough, as typically occurs with ACE inhibitors. The incidence of cough was similar in placebo patients (0.6%) and patients treated with Rasilez (0.9%).
The frequency of adverse reactions listed below is defined using the following convention: Very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥ 1/10 000 to < 1/1000; very rare: < 1/10 000, including isolated cases. Within each frequency grouping, adverse reactions are presented in the order of decreasing severity.

Gastrointestinal disorders
Common: Diarrhoea.

Skin disorders
Uncommon: Rash.

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

Haemoglobin and haematocrit
Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/litre and 0.16 volume percent, respectively) were observed. No patients needed to discontinue therapy because of anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers.

Serum potassium
Increases in serum potassium were minor and rare in patients with essential hypertension treated with Rasilez alone (0.9%, versus 0.6% with placebo). However, in one study where Rasilez was used in combination with an ACE inhibitor in diabetic patients, increases in serum potassium were more frequent (5.5%). Therefore, as with any agent acting on the renin-angiotensin system, routine monitoring of electrolytes and renal function is indicated in diabetic patients using Rasilez.

Overdose
Limited data are available on overdosage in humans. The most likely manifestation of overdosage would be hypotension, due to the antihypertensive effect of aliskiren. If symptomatic hypotension should occur, supportive treatment should be initiated.

Properties and Actions
ATC code: C09XA02
Pharmacotherapeutic group: renin inhibitor

Mechanism of action
Rasilez is a potent, selective, direct, orally active, non-peptide inhibitor of human renin. It acts on the renin-angiotensin system (RAS) by binding to the enzyme renin, thereby blocking the conversion of angiotensinogen to angiotensin I. In this way, it reduces renin activity and plasma levels of angiotensin I and angiotensin II.

Pharmacodynamics
Renin is secreted by the kidney in response to a decrease in blood volume and renal perfusion. This reaction initiates a cycle that involves the renin-angiotensin system (RAS) and a homeostatic feedback loop. Renin cleaves angiotensinogen to generate the inactive decapeptide angiotensin I (Ang I). Ang I is converted by angiotensin converting enzyme (ACE) and non-ACE pathways to the active octapeptide angiotensin II (Ang II). Ang II is a potent vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and presynaptic nerve endings. It also promotes aldosterone secretion and sodium reabsorption. The net result of these actions is an increase in blood pressure. Chronic Ang II elevation causes the release of markers and mediators of inflammation and fibrosis, ultimately leading to end-organ damage. Ang II also inhibits renin release, thus providing negative feedback. Elevated plasma renin activity (PRA) is independently associated with increased cardiovascular risk in hypertensive and normotensive patients.
All substances that inhibit this system, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory increase in plasma renin concentrations. When this increase occurs during treatment with an ACE inhibitor or an angiotensin II receptor blocker (ARB), it is accompanied by increased PRA. During treatment with aliskiren, by contrast, the effects on the feedback loop are neutralized, with PRA, Ang I and Ang II all decreased as a result, regardless of whether aliskiren is used as monotherapy or in combination with other antihypertensives.
Treatment with Rasilez decreases PRA in hypertensive patients. In clinical studies the decrease in PRA ranged from 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents.

Clinical efficacy
In hypertensive patients, Rasilez achieves a sustained dose-dependent reduction in both systolic and diastolic blood pressure. Once-daily administration of Rasilez at doses of 150 mg and 300 mg provided effective blood pressure reduction over the entire 24 hour dose interval (maintaining benefit in the early morning), with a trough-to-peak ratio for diastolic blood pressure of 98% for the 300 mg dose. After 2 weeks, 85 to 90% of the maximum blood-pressure-lowering effect was observed. The blood-pressure-lowering effect was sustained in patients treated for up to one year, as was shown by a statistically significant difference from placebo four weeks after randomized withdrawal. 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.
There has been no evidence of first-dose hypotension or of an effect on pulse rate in patients treated in controlled studies. Severe hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with Rasilez. Hypotension was also uncommonly (< 1%) seen during combination therapy with other antihypertensive agents.
In controlled studies, the blood-pressure-lowering effect of Rasilez in combination with hydrochlorothiazide or ramipril was additive, and the combinations were well tolerated. A lower incidence of cough was seen with the combination of Rasilez and the ACE inhibitor ramipril than with ramipril alone (1.8% with aliskiren/ramipril vs. 4.7% with ramipril). In patients who did not adequately respond to 5 mg of the calcium channel blocker (CCB) amlodipine, Rasilez 150 mg likewise had an additive blood-pressure-lowering effect and was well tolerated. Efficacy was similar to that with 10 mg amlodipine, but the incidence of oedema was lower (2.1% with aliskiren/amlodipine vs. 11.2% with amlodipine). Co-administration with the ARB valsartan was well tolerated.
Rasilez shows a blood-pressure-lowering effect similar to that of other classes of antihypertensive agents, including ACE inhibitors, ARBs and CCBs.
The antihypertensive effect of Rasilez was compared with that of hydrochlorothiazide (HCTZ) in a 26 week randomized, double-blind study with the option of adding amlodipine. After 12 weeks of monotherapy with 300 mg aliskiren or 25 mg HCTZ, the reduction from baseline systolic/diastolic blood pressure was 17.0/12.3 mmHg for aliskiren and 14.4/10.5 mmHg for HCTZ. At endpoint, systolic/diastolic blood pressure had decreased by 19.6/14.2 mmHg from baseline following treatment with 300 mg aliskiren and by 17.9/13.0 mmHg following treatment with 25 mg HCTZ.
Rasilez monotherapy has proven safe and effective in diabetic hypertensive patients. In combination with ramipril, Rasilez provided additional blood pressure reduction, as compared with the monotherapies.
In obese hypertensive patients who were inadequately treated with HCTZ, Rasilez provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan or amlodipine.
The antihypertensive effect of Rasilez was independent of age, sex, body mass index and ethnicity.

Pharmacokinetics
Absorption
Following oral administration, peak plasma concentrations of aliskiren were reached after 1-3 hours. The absolute bioavailability of aliskiren is 2.6%. Food reduces C_{max} and exposure (AUC) but has only a minimal impact on pharmacodynamics, so aliskiren can be taken with or without food. Steady-state plasma levels, which are reached after 5–7 days of once-daily administration, are approximately twice as high as plasma levels reached after the initial dose.

Distribution
Aliskiren undergoes uniform systemic distribution after oral administration. 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.

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

Elimination
The mean elimination half-life is about 40 hours (34–41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (91%). Approximately 0.6% of the dose is recovered in the urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 litres/hour.

Linearity / non-linearity
The peak plasma concentrations (C_{max}) and exposure (AUC) of aliskiren increase linearly with increasing dose over the range of 75–600 mg.

Pharmacokinetics in special patient populations
Patients with renal impairment
The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. Following single-dose administration, and at steady state, the AUC and C_{max} of aliskiren in subjects with renal impairment were 0.8 to 2 times higher than in healthy subjects. The observed changes, however, did not correlate with the severity of renal impairment. No data are available on the use of Rasilez in dialysis patients.

Patients with hepatic impairment
The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe hepatic impairment.

Elderly patients
The AUC in the elderly (> 65 years of age) is 50% higher than in younger people.

Children and adolescents
No pharmacokinetic data are available in children or adolescents.

Preclinical data
Carcinogenicity
Carcinogenic potential was assessed in a 2 year study in rats and a 6 month study in transgenic mice. No carcinogenic potential was detected. Inflammatory and proliferative changes were observed in the lower gastrointestinal tract in both species at doses of 750 to 1500 mg/kg/day. In rats given doses of 1500 mg/kg/day, one colonic adenoma and one caecal adenocarcinoma were not statistically significant. These findings were attributed to the known irritation potential of aliskiren. Following a dose of 300 mg, safety margins in humans were 9–11, based on faecal concentrations, and 6, based on mucosal concentrations, as compared with the no-observed-adverse-effect level (NOAEL) of 250 mg/kg/day in the rat carcinogenicity study.

Mutagenicity
Aliskiren showed no mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies. The studies included *in vitro* assays in bacterial and mammalian cells and *in vivo* assessments in rats.

Reproductive toxicity
Reproductive toxicity studies with aliskiren did not reveal any evidence of embryo/fetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats and 100 mg/kg/day in rabbits. Fertility, prenatal development and postnatal development were unaffected in rats given doses up to 250 mg/kg/day. On a mg/m² basis, the doses in rats and rabbits were 6–16 and 6 times higher, respectively, than the maximum recommended human dose of 300 mg (calculations based on a 50 kg patient).

Other information
Shelf-life
See folding box
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box
Store in the original package.
Keep out of the reach of children.

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
March 2009

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8 December 2009

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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