

New Zealand Data Sheet

RASILEZ®

Aliskiren

150 mg and 300 mg film-coated tablets.

Qualitative and quantitative composition

The active substance is 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate (INN – Aliskiren).

One film-coated tablet contains 150 mg or 300 mg aliskiren hemifumarate.

For a full list of excipients, see List of excipients.

Pharmaceutical form

Film-coated tablet.

Clinical particulars

Therapeutic indications

Treatment of hypertension.

Dosage and method of administration

Hypertension

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 within 2 weeks (85 to 90%) after initiating therapy with 150 mg once daily.

Rasilez may be used alone or in combination with other antihypertensive agents. It must not be used in combination with Angiotensin Converting Enzyme Inhibitors (ACEi) or Angiotensin II Receptor Blockers (ARB) in patients with type 2 diabetes mellitus.

Rasilez may be administered without regard to meals.

Use in elderly patients (over 65 years)

No initial dosage adjustment is required for elderly patients.

Use in renal impairment

No initial dose adjustment is required for patients with mild to severe renal impairment (see Special warnings and precautions for use and Pharmacokinetic properties). Rasilez is not recommended in patients with severe renal impairment (GFR < 30 mL/min).

Use in hepatic impairment

No initial dosage adjustment is required for patients with mild to severe hepatic impairment (see Pharmacokinetic properties).

Use in children and adolescents

The safety and efficacy of Rasilez has not been established in children and adolescents (below 18 years of age) and therefore Rasilez is not recommended in this population.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of aliskiren with ARBs or ACEi in patients with type 2 diabetes mellitus.

Special warnings and precautions for use

Pregnancy

Aliskiren was not teratogenic in standard animal tests and it had no treatment-related effects in the prenatal development study in rats (see Preclinical Safety data). Other substances that act directly on the renin-angiotensin system have however been associated with serious fetal

malformations and neonatal death. As no specific clinical studies have been performed, aliskiren is therefore not recommended for use during pregnancy (see Pregnancy and lactation) or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the Renin-angiotensin system (RAS) should counsel women of childbearing potential about the potential risk of these agents during pregnancy. When pregnancy is detected, Rasilez should be discontinued as soon as possible.

Sodium and/or volume depleted patients

In patients with marked volume- and/or salt-depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Rasilez. This condition should be corrected prior to administration of Rasilez, or the treatment should start under close medical supervision.

Patients with pre-existing renal impairment

In clinical studies, Rasilez has not been studied in hypertensive patients with severe renal dysfunction (creatinine ≥ 150 $\mu\text{mol/L}$ for women and ≥ 177 $\mu\text{mol/L}$ for men and/or estimated GFR < 30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension. Use of aliskiren alone or concomitantly with another agent acting on the RAAS is not recommended in patients with severe renal impairment (GFR < 30 mL/min). Other agents that act on the renin-angiotensin system may increase potassium, serum creatinine and blood urea nitrogen in these patients and a similar effect may be anticipated with Rasilez.

Patients with renal artery stenosis

No data are available on the use of Rasilez in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Since other drugs that affect the RAAS may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, caution should therefore be exercised in these patients.

Risk for renal dysfunction/Serum electrolyte changes

As for other agents that act on the RAAS, aliskiren may increase potassium, serum creatinine and blood urea nitrogen. Increases in serum potassium may be exacerbated by the concomitant use of other agents acting on the RAAS or use of NSAIDs. Patients with diabetes mellitus are at an increased risk of hyperkalemia during aliskiren therapy.

Worsening of renal function may occur in patients receiving aliskiren and other RAAS agents or NSAIDs concomitantly, or in those with pre-existing renal disease, diabetes mellitus or with other conditions pre-disposing to renal dysfunction such as hypovolemia, heart failure or liver disease.

Close monitoring of serum electrolytes to detect possible electrolyte (potassium) imbalances is advised at initiation of therapy with Rasilez and periodic monitoring thereafter.

Concomitant use with cyclosporin A

The concomitant use of aliskiren with cyclosporin or itraconazole, potent P glycoprotein inhibitors, is not recommended (see Interaction with other medicinal products and other forms of interaction).

Angioedema

Angioedema has been reported during treatment with aliskiren. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. Patients should discontinue the treatment promptly and should report to the physician any signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips, tongue).

Interaction with other medicinal products and other forms of interaction

Rasilez has a low potential for interactions with other medicinal products.

Compounds that have been investigated in clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, irbesartan, digoxin, ramipril and hydrochlorothiazide and no interactions have been identified. Co-administration of aliskiren with either valsartan (decrease of 28%), metformin (decrease of 28%), amlodipine (increase of 29%) or cimetidine (increase of 19%) resulted in between 20% and 30% change in C_{max} or AUC of aliskiren. Co-administration of aliskiren had no significant impact on atorvastatin, valsartan, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for aliskiren or these co-administered medications is necessary.

CYP 450 interactions: Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A). Aliskiren does not induce CYP3A4. Aliskiren is metabolised minimally by the cytochrome P450 enzymes, therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce, or are metabolised by these enzymes.

P glycoprotein interactions

In vitro studies indicate that MDR1(Pgp) was found to be the major efflux transporter involved in absorption and disposition of aliskiren. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

Pgp substrates or weak- inhibitors: No relevant interactions with atenolol, digoxin, amlodipine, and cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and C_{max} increased by 50%.

Moderate Pgp inhibitors: Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in a 80% increase in plasma levels of aliskiren (AUC and C_{max}). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and C_{max} of aliskiren by ~2-fold. 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. As a result no dose adjustment for aliskiren is necessary.

Potent Pgp inhibitors: A single dose drug interaction study in healthy subjects has shown that cyclosporin (200 and 600 mg) increases C_{max} of aliskiren 75 mg by approximately 2.5 fold and the AUC by approximately 5 fold. 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, the concomitant use of these drugs with aliskiren is not recommended (see Special warnings and precautions for use).

Furosemide: When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by 28% and 49% respectively. It is therefore recommended that the effects be monitored when initiating and adjusting furosemide therapy to avoid possible under-dosing.

Non-steroidal anti-inflammatory drugs (NSAIDs): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs with agents acting on the renin-angiotensin system may result in deterioration of renal function, including possible acute renal failure, which is usually reversible. Concomitant administration of NSAIDs may attenuate the antihypertensive effect of agents acting on the renin-angiotensin system, including aliskiren.

Potassium and potassium sparing diuretics: Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of aliskiren with the following medicines may lead to increases in serum potassium: Potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium. If comedication is considered necessary, caution is advisable (see Adverse effects).

Pregnancy and lactation

Pregnancy

There are no adequate data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see Preclinical Safety data). Other substances that act directly on the renin-angiotensin system have however been associated with serious fetal malformations and neonatal death. As for any medicine that acts directly on the RAS, Rasilez should not be used during pregnancy (see Special warnings and precautions for use) or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Rasilez should be discontinued as soon as possible.

Lactation

It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the Rasilez, taking into account the importance of Rasilez to the mother.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse effects

Rasilez has been evaluated for safety in more than 7800 patients, including over 2300 treated for over 6 months, and more than 1200 for over 1 year. The incidence of adverse events showed no association with gender, age, body mass index, race or ethnicity. Treatment with Rasilez was well tolerated with an overall incidence of adverse experiences similar to placebo up to 300 mg. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The most common adverse drug reaction is diarrhea.

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 (0.6%) and Rasilez (0.9%) patients.

Angioedema has occurred during treatment with aliskiren. In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren (0.3%) with rates comparable to treatment with placebo (0.4%) or hydrochlorothiazide (0.2%).

The adverse drug reactions (table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$), including isolated report. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Gastrointestinal disorders	
Common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
Uncommon	Severe cutaneous adverse reactions including Stevens Johnson syndrome and toxic epidermal necrolysis

Immune system disorders	
Rare:	Hypersensitivity
Investigations	
Common	Hyperkalemia
Renal and urinary disorders	
Uncommon:	Renal impairment
Rare:	Renal failure
Nervous system disorders	
Common:	Dizziness
Vascular disorders	
Uncommon:	Hypotension

Laboratory findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of Rasilez. In clinical studies in hypertensive patients, Rasilez had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose or uric acid.

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

Serum potassium: Increases in serum potassium were minor and infrequent in patients with essential hypertension treated with Rasilez alone. However, in one study where Rasilez was used in combination with an angiotensin converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) (see Contraindications). Monitoring of electrolytes and renal function is indicated when using Rasilez (see Special warnings and precautions for use).

Post-marketing experience: Peripheral edema; blood creatinine increased (frequency unknown).

Overdose

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

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

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Renin inhibitor, ATC code: C09XA02.

Mechanism of action

Rasilez is an orally active, non-peptide, potent and selective direct inhibitor of human renin. Rasilez targets the renin-angiotensin system (RAS) at the point of activation by binding to the enzyme renin, thereby blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of plasma renin activity (PRA), angiotensin I and angiotensin II.

Pharmacodynamic effects

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the renin angiotensin system (RAS) and a homeostatic feedback loop. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by

angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Chronic increases in Ang II result in the expression of markers and mediators of inflammation and fibrosis that are associated with end organ damage. Ang II also inhibits renin release, thus providing a negative feedback to the system. Elevated plasma renin activity (PRA) has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients.

All agents that inhibit this system, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, it is accompanied by increased levels of PRA. During treatment with aliskiren, however, the feedback loop effects are neutralised. As a result, PRA, Ang I, and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

Treatment with Rasilez decreases PRA in hypertensive patients. In clinical trials, PRA reductions ranged from approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive drugs.

Hypertension

In hypertensive patients Rasilez causes a dose-dependent, long-lasting reduction in both systolic and diastolic blood pressure. Once daily administration of Rasilez at doses of 150 mg and 300 mg provided an effective reduction in blood pressure over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of 98% for the 300 mg dose. After 2 weeks, 85 to 90% of the maximal blood-pressure-lowering effect was observed. The blood-pressure-lowering effect was sustained in patients treated for up to one year as demonstrated by a statistically significant difference from placebo 4 weeks after randomised withdrawal. With cessation of treatment, blood pressure gradually returned toward 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 and no effect on pulse rate in patients treated in controlled trials. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with Rasilez alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents.

In controlled studies, the blood pressure-lowering-effect of Rasilez in combination with either hydrochlorothiazide or ramipril was additive and the combinations were well tolerated. The combination of Rasilez and the ACE inhibitor ramipril had a lower incidence of cough than ramipril (aliskiren/ramipril 1.8% vs. ramipril 4.7%). Rasilez 150 mg also had an additive blood-pressure-lowering effect and was well tolerated in patients who had not adequately responded to a 5 mg dose of the calcium channel blocker amlodipine. The efficacy was similar to that achieved with 10 mg amlodipine but there was a lower incidence of edema (aliskiren/amlodipine 2.1% vs. amlodipine 11.2%). Co-administration with the ARB valsartan was well tolerated.

Rasilez is comparable in blood-pressure-lowering efficacy to other classes of antihypertensive agent including ACEIs, ARBs and CCBs.

The antihypertensive effect of Rasilez and hydrochlorothiazide (HCTZ) were compared in a 26-week randomised, double-blind, parallel group study with optional addition of amlodipine. After 12 weeks on aliskiren 300 mg and HCTZ 25 mg monotherapy the blood pressure reduction (systolic/diastolic) from baseline was 17.0/12.3 mmHg for aliskiren and 14.4/10.5 mmHg for HCTZ. At endpoint the blood pressure reduction (systolic/diastolic) from

baseline was 19.6/14.2 mmHg with the aliskiren 300 mg regimen and 17.9/13.0 mmHg with the HCTZ 25 mg regimen.

In diabetic hypertensive patients, Rasilez as monotherapy was safe and effective. In combination with ramipril, Rasilez provided additive blood pressure reductions compared to the component monotherapies.

In obese hypertensive patients inadequately treated with HCTZ add-on treatment with Rasilez provided additional blood pressure reduction that was comparable to the blood pressure reductions with add-on treatment with irbesartan or amlodipine.

The antihypertensive effects of Rasilez were independent of age, gender, body mass index and ethnicity.

In a 3-month study of 302 patients with a current diagnosis or history of hypertension and mild stable heart failure, all of whom were receiving standard therapy for stable heart failure (ACE inhibitor or ARB, a beta blocker and for a third of patients an aldosterone antagonist), addition of Rasilez 150 mg was well tolerated. B-type natriuretic peptide (BNP) levels were reduced by 25% in the Rasilez arm compared to placebo.

Efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month 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. The differences in both systolic and diastolic blood pressure were statistically significant. After 12 weeks, 46.3 % of patients required add-on treatment with hydrochlorothiazide in the aliskiren-regimen compared to 55.5 % of patients receiving a ramipril-based regimen. After 22 weeks 11.5 % of patients required add-on treatment with amlodipine in the aliskiren regimen compared to 15.7 % of patients receiving a ramipril-based regimen. 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 %). The most common adverse event for the aliskiren-regimen was diarrhea (6.6 % vs. 5.0 % for the ramipril-regimen).

In a double-blind, randomized, active-controlled study in which efficacy was assessed in 1181 patients, once-daily administration of aliskiren 300 mg with amlodipine 10 mg and HCTZ 25 mg produced statistically significant mean blood pressure reductions (systolic/diastolic) of 37.9/20.6 mmHg compared to 31.4/18.0 mmHg with aliskiren/amlodipine combination (300/10 mg), 28.0/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 30.8/17.0mmHg with amlodipine/hydrochlorothiazide (10/25 mg) in patients with moderate to severe hypertension. In patients with severe hypertension (SBP ≥ 180 mmHg), the reduction in blood pressure for the triple combination of aliskiren, HCTZ and amlodipine was 49.5/22.5 mmHg compared to 38.1/17.6 mmHg with aliskiren/amlodipine combination (300/10 mg), 33.2/14.3 mmHg with aliskiren/hydrochlorothiazide (300/25 mg) and 39.9/17.8 mmHg with amlodipine/hydrochlorothiazide (10/25 mg). The combination of aliskiren/amlodipine/HCTZ was generally well-tolerated and the most commonly reported adverse event was peripheral oedema.

Long-term gastrointestinal (GI) safety and tolerability of aliskiren was evaluated in a 54 week, randomized, double-blind, active controlled (ramipril) study in patients with essential hypertension at least 50 years of age. There were no statistically significant differences in the relative risk of the composite endpoint or any of its components (hyperplastic polyps, inflammatory polyps, adenomatous polyps, and carcinoma), as assessed by colonoscopy,

following one year of treatment with aliskiren 300 mg daily compared to ramipril 10 mg daily with an overall relative risk of 1.03. A doubling of the relative risk of the compository endpoint (primary study outcome) was excluded with $p < 0.0001$. Mucosal hyperplasia scores, dysplasia score, and severity of inflammation were low at baseline and no increases were observed in either of the two treatment groups. No pathologic effect of aliskiren on the colorectum was detected.

Pharmacokinetic properties

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1 to 3 hours. The absolute bioavailability of aliskiren is 2.6%. Food reduces the C_{max} and exposure (AUC) but has minimal impact on pharmacodynamics thus can be taken without respect to food. Steady-state-plasma concentrations are reached within 5 to 7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Distribution

Aliskiren is evenly distributed systemically after oral administration. Following intravenous administration, mean volume of distribution at steady state is approximately 135 L indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47 to 51%) and independent of the concentration.

Metabolism and elimination

The mean elimination half-life is about 40 hours (range 34 to 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, the mean plasma clearance is approximately 9 L/h.

Linearity / non-linearity

Peak plasma concentrations (C_{max}) and exposure (AUC) of aliskiren increase linearly with increasing dose over the range of 75 to 600 mg.

Characteristics in patients

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

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-fold compared to those 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 initial dosage adjustment of Rasilez is required in patients with mild to severe renal impairment however caution should be exercised in severely renally impaired patients.

The pharmacokinetics of aliskiren were evaluated in patients with End Stage Renal Disease receiving hemodialysis. 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 hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis.

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

Also no initial dose adjustment of Rasilez is required for elderly patients.

Preclinical safety data

Carcinogenicity

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic mouse study. No carcinogenic potential was detected. Inflammatory and proliferative changes were observed in the lower gastro-intestinal tract at doses of 750 or 1500 mg/kg/day in both species. One colonic adenoma and one cecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant. These findings were attributed to the known irritation potential of aliskiren. The results from a subsequent 104-week oral toxicity study in marmoset monkeys show the absence of any treatment-related histopathological changes in the gastro-intestinal tract at doses of 10 and 20 mg/kg/day.

Safety margins obtained in humans at the dose of 300 mg were 9-11-fold based on fecal concentrations or 6-fold based on mucosa concentrations in comparison with the no-observed-adverse-effect-level (NOAEL) of 250 mg/kg/day in the rat carcinogenicity study.

Mutagenicity

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

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofetal 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 dose in rats and rabbits are 6-16 and 6 times, respectively, the maximum recommended human dose (300 mg) on a mg/m² basis (calculations assume an 50 kg patient).

Pharmaceutical particulars

List of excipients

Crospovidone; magnesium stearate; microcrystalline cellulose; povidone; silica, colloidal anhydrous; hypromellose; macrogol; talc; iron oxide, black (E 172); iron oxide, red (E 172); titanium dioxide (E 171).

Incompatibilities

Not applicable.

Shelf life

2 years.

Special precautions for storage

Do not store above 30°C.

Store in the original package.

Rasilez tablets must be kept out of the reach and sight of children.

Nature and contents of container

PA/Alu/PVC blisters.

Instructions for use/handling

No special requirements.

Medicine classification

Prescription Medicine

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