פורמט עלון זה נקבע ע״י משרד הבריאות ותוכנו נבדק ואושר על ידו ביוני2015.

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT
Rasilez 150mg, Rasilez 300 mg
film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 or 300 mg aliskiren.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Rasilez 150 mg: Light-pink, biconvex, round tablet with beveled edges, imprinted “IL” on one side and “NVR” on the other side.
Rasilez 300 mg: Light-red, biconvex, ovaloid tablet with beveled edges, imprinted “IU” on one side and “NVR” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of essential hypertension.

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

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

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

Rasilez should be taken with a light meal once a day, preferably at the same time each day. Grapefruit juice should not be taken together with Rasilez.

Renal impairment

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

Hepatic impairment

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

Elderly patients (over 65 years)

No adjustment of the initial dose is required for elderly patients.

Pediatric patients (below 18 years of age)

Rasilez is contraindicated in children less than 2 years of age (see sections 4.3, 4.4 and 5.3). Rasilez should not be used in children aged 2 to less than 6 years of age because of safety concern for potential aliskiren overexposure (see sections 4.4, 5 and 4.3)
Limited data are available in children 6 to less than 18 years of age and the safety and efficacy of Rasilez has not been established in this age group. Use of Rasilez is not recommended in this population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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 or itraconazole, potent P-gp inhibitors, and other potent P-gp inhibitors (quinidine), is contraindicated (see section 4.5).
- The concomitant use of Rasilez with ARBs or ACEIs 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).
- Pediatric patients less than 2 years of age (see sections 4.4 and 5.3)

4.4 Special warnings and precautions for use

Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association [NYHA] functional class III-IV).

In the event of severe and persistent diarrhoea, Rasilez therapy should be stopped.

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.

Anaphylactic reactions and angioedema

Hypersensitivity reactions such as anaphylactic reactions and angioedema have been reported during treatment with aliskiren (see section 4.8). In controlled clinical trials, angioedema occurred rarely during treatment with aliskiren with rates comparable to treatment with placebo or hydrochlorothiazide. Anaphylactic reactions have been reported from post-marketing experience with unknown frequency. Special caution is necessary in patients with a predisposition for hypersensitivity. Patients should discontinue the treatment promptly and should be informed to report to the physician any signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue). Appropriate therapy and monitoring measures should be initiated.

Angioedema

As with other agents acting on the renin-angiotensin 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 medicines that can cause angioedema, including RAAS blockers (ACEI orARBs) (see section 4.8).

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

If angioedema occurs, Rasilez should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patient airways should be provided.

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with Rasilez in the following cases:

- Patients with marked volume depletion or
- Patients with salt depletion or
- Combined use of aliskiren with other agents acting on the RAAS (see section 4.5)

The volume- or salt depletion 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 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 glomerular filtration rate (GFR) < 30 ml/min/1.73m^2), history of dialysis, nephrotic syndrome or renovascular hypertension.

Use of aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min/1.73m^2).

As for other agents acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe prolonged diarrhoea, prolonged vomiting etc.), heart disease, liver disease 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.

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (GFR ≥ 30 mL/min/1.73m^2) (see sections 4.4 and 5.2).

Patients with renal artery stenosis

No controlled clinical data are available on the use of Rasilez in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, as with other agents acting on the renin-angiotensin 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.

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 non-steroidal anti-inflammatory drugs (NSAIDs). Patients with diabetes mellitus are at 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.

Pediatric patients (less than 18 years of age)

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 and 5.3). Therefore, Rasilez is contraindicated in children less than 2 years of age and should not be used in children 2 to less than 6 years of age.

Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6 to less than 18 years of age (see sections 4.8 and 5).

Use of Rasilez in this age group is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Compounds that have been investigated in clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate, ramipril and hydrochlorothiazide. No pharmacokinetic interactions have been identified. For pharmacodynamic interactions with NSAIDs and cox inhibitors compounds - see below.

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

Digoxin bioavailability may be slightly decreased by Rasilez.

Preliminary data suggest that irbesartan may decrease Rasilez AUC and Cmax.

In experimental animals, it has been shown that P-gp is a major determinant of Rasilez bioavailability. Inducers of P-gp (St. John's wort, rifampicin) might therefore decrease the bioavailability of Rasilez.

CYP 450 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 with CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see P-glycoprotein interactions below).

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

P-gp 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 Cmax increased by 50%.

Moderate P-gp inhibitors

Co-administration of ketoconazole (200 mg) with aliskiren (300 mg) resulted in an 80% increase in plasma levels of aliskiren (AUC and Cmax). Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. The change in plasma levels of aliskiren in the presence of 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, have been found to be well tolerated in controlled clinical trials. Yet, P-gp inhibitors are expected to increase tissue concentrations more than plasma concentrations. Therefore, caution should be exercised when aliskiren is administered with ketoconazole or other moderate pgp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

P-gp potent inhibitors

A single dose drug interaction study in healthy subjects has shown that ciclosporin (200 mg and 600 mg) increases Cmax of aliskiren 75 mg by 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 Cmax of aliskiren (150 mg) by 6.5 fold and 5.8 fold, respectively. Co-administration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and Cmax of aliskiren by ～2-fold.Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

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 Grapefruit juice).

Furosemide

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 (60mg/day) co-administration with aliskiren (300 mg/day) to patients with heart failure, urinary sodium excretion and 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. In patients treated with both aliskiren and oral furosemide, it is therefore recommended that the effects of furosemide be monitored when initiating or adjusting the dose of furosemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload.

Non-steroidal anti-inflammatory drugs (NSAIDs) including cox inhibitors

As with other agents acting on the renin-angiotensin 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.

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.

Grapefruit juice

Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration 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. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with Rasilez.

Warfarin

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

Food intake

Meals with a high fat content have been shown to reduce the absorption of Rasilez substantially.

4.6 Pregnancy and lactation

Pregnancy

There are no data on the use of aliskiren in pregnant women. Rasilez 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, Rasilez should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Rasilez should be discontinued accordingly.

Lactation

It is not known whether aliskiren is excreted in human milk. Rasilez was secreted in the milk of lactating rats. Its use is therefore not recommended in women who are breast-feeding.

Fertility

There is no available data on the effect of aliskiren on human fertility. No impairment in fertility was demonstrated in studies performed in rats (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Rasilez has negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or weariness may occasionally occur when taking Rasilez.

4.8 Undesirable effects

Summary of the safety profile

Rasilez has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over 1 year. The incidence of adverse reactions showed no association with gender, age, body mass index, race or ethnicity. Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions:

The adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

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

*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more marked hepatic dysfunction.

**Including one case of 'liver failure fulminant' reported in the post-marketing experience, for which a causal relationship with aliskiren cannot be excluded.

Description of selected adverse reactions
Hypersensitivity reactions including anaphylactic reactions and angioedema 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 medicines known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

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

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

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

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

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

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

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

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

Paediatric population
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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; renin inhibitor, ATC code: C09XA02.

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

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (ACEI and ARBs) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients. 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 Rasilez 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. Rasilez has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

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

Combination therapy studies are available for Rasilez added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. Rasilez induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide. In patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of Rasilez 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing amlodipine dose to 10 mg, but had a lower incidence of oedema (aliskiren 150 mg/amlodipine 5 mg 2.1% vs. amlodipine 10 mg 11.2%).

In obese hypertensive patients who did not adequately respond to HCTZ 25 mg, add-on treatment with Rasilez 300 mg provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan 300 mg or amlodipine 10 mg. In diabetic hypertensive patients, Rasilez provided additive blood pressure reductions when added to ramipril, while the combination of Rasilez and ramipril had a lower incidence of cough (1.8%) than ramipril (4.7%).

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 Rasilez alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 3-month study of 302 patients with mild stable heart failure, all of whom were receiving standard therapy for stable heart failure, 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. However the clinical significance of this reduction is unknown.

Beneficial effects of Rasilez on mortality and cardiovascular morbidity and target organ damage are currently unknown.

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 1,181 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/hydrochlorothazide (300/25 mg) and 30.8/17.0 mmHg 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 alskiren/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.

Cardiac electrophysiology

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

5.2 Pharmacokinetic properties

Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce Cmax by 85% and AUC by 70%. 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 approximately135 liters , indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Metabolism 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, the mean plasma clearance is approximately 9 l/h.

Linearity/non-linearity

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

Characteristics in patients

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

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 Cmax 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

Rasilez is required in patients with mild to moderate renal impairment. Rasilez should be avoided in patients with severe renal impairment (GFR) < 30 ml/min/1.73 m^2).

The pharmacokinetics of aliskiren were evaluated in patients with End Stage Renal Disease receiving henodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in Cmax 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 in warranted in ESRD patients receiving hemosialysis. Rasilez should be avoided in patients with severe renal impairment (GFR) < 30 ml/min/1.73 m^2) (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.

In a pharmacokinetic study of aliskiren treatment in 39 pediatric hypertensive patients aged 6 to less than 18 years, given daily doses of 2 mg/kg or 6 mg/kg aliskiren, administered as mini-tablets (3.125 mg/mini-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 *in vitro* MDR1 (P-gp) human tissue study suggested an age and tissue dependent pattern of MDR1 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 fetuses, neonates, and infants up to 23 months.

The age at which MDR1 (P-gp) is mature cannot be determined. There is a potential for aliskiren overexposure in children with an immature MDR1 (see "Transporters" above and sections 4.2, 4.3 and 5.3).

5.3 Preclinical safety data

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. 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. 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 toxicity studies in rats indicated that excessive aliskiren exposure (>400 fold higher in 8-day-old rats compared with adult rats) and associated toxicity are caused by immature MDR1. This suggests that in pediatric patients with immature MDR1, there is a potential for aliskiren overexposure and associated toxicity (see section 5).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Magnesium stearate
Cellulose, microcrystalline
Povidone
Silica, colloidal anhydrous
Hypromellose
Macrogol 4000
Talc
Iron oxide, black
Iron oxide, red
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage
Store below 30°C. Store in the original package. Protect from moisture.

6.4 Nature and contents of container
Blisters.

6.5 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Novartis Farma S.p.A, Torre Annunziate, Italy
For Novartis Pharma AG, Basel, Switzerland.

8. LICENSE HOLDER
Novartis Pharma Services AG
36 Shacham St., Petach-Tikva.

9. REGISTRATION NUMBERS
Rasilez 150mg: 138 80 31611
Rasilez 300mg: 138 81 31612