NOVARTIS

Rasilez HCT®

Composition
Active substances: Aliskiren (as aliskiren hemifumarate), hydrochlorothiazide

Excipients:
Rasilez HCT 150 mg/12.5 mg: Cellulose, microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, titanium dioxide (E 171)
Rasilez HCT 150 mg/25 mg: Cellulose, microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, iron oxide red (E 172) iron oxide yellow (E172) titanium dioxide (E 171)
Rasilez HCT 300 mg/12.5 mg: Cellulose, microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, iron oxide black (E 172), iron oxide red (E 172), titanium dioxide (E 171)
Rasilez HCT 300 mg/25 mg: Cellulose, microcrystalline, crospovidone, lactose monohydrate, wheat starch, povidone, magnesium stearate, silica colloidal anhydrous, talc, hypromellose, macrogol, iron oxide red (E 172), iron oxide yellow (E 172), titanium dioxide (E 171)
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit
Rasilez HCT 150 mg/12.5 mg
Film-coated tablets containing 150 mg aliskiren and 12.5 mg hydrochlorothiazide
Rasilez HCT 150 mg/25 mg
Film-coated tablets containing 150 mg aliskiren and 25 mg hydrochlorothiazide
Rasilez HCT 300 mg/12.5 mg
Film-coated tablets containing 300 mg aliskiren and 12.5 mg hydrochlorothiazide
Rasilez HCT 300 mg/25 mg
Film-coated tablets containing 300 mg aliskiren and 25 mg hydrochlorothiazide

Indications / Potential uses
Treatment of essential hypertension.
Rasilez HCT is indicated in patients whose blood pressure is not adequately controlled by monotherapy.
Rasilez HCT is indicated as alternative treatment in patients already taking equivalent doses of aliskiren and hydrochlorothiazide as separate tablets.
Rasilez HCT is indicated in the initial treatment of hypertension in patients with moderately to severely increased blood pressure (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg.

Dosage / Administration
Rasilez HCT may be taken without regard to meals.

Patients not adequately treated with monotherapy
Patients whose blood pressure is not adequately controlled by aliskiren or hydrochlorothiazide monotherapy may be switched to combination therapy with Rasilez HCT. The recommended starting dose of Rasilez HCT is 150 mg/12.5 mg once daily.
In patients whose blood pressure cannot be adequately lowered after 2-4 weeks, the dose may be titrated up to a maximum of 300 mg/25 mg aliskiren/hydrochlorothiazide. Dosing should be individualized and adjusted according to the patient's clinical response.

Patients adequately treated with separate tablets of aliskiren and hydrochlorothiazide
Patients already receiving aliskiren and hydrochlorothiazide as separate tablets may be switched to a single tablet of Rasilez HCT containing the same doses of the active components.

Initial treatment of patients with moderately to severely increased blood pressure (≥160 mmHg and/or ≥100 mmHg)
For initial treatment, the recommended starting dose is 150 mg/12.5 mg once daily. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to a maximum of 300 mg/25 mg aliskiren/hydrochlorothiazide. Dosing should be individualized and adjusted according to the patient's clinical response.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min/1.73 m^2; see "Pharmacokinetics"). Due to the hydrochlorothiazide component, Rasilez HCT should be used only with special caution in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2; see "Contraindications" and "Warnings and precautions").

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see "Pharmacokinetics"). Due to the hydrochlorothiazide component, Rasilez HCT should be used with particular caution in patients with severe hepatic impairment (see "Warnings and precautions").

Elderly patients (over 65 years)
No adjustment of the initial dose is required for elderly patients (see "Pharmacokinetics").

Children and adolescents (under 18 years)
Rasilez HCT is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy (see "Pharmacokinetics").

Contraindications
Hypersensitivity to the active substances aliskiren or hydrochlorothiazide, to sulphonamide derivatives or to any of the excipients of Rasilez HCT.
History of angioedema with aliskiren; hereditary or idiopathic angioedema.
Pregnancy and lactation (see "Pregnancy / Lactation").
Concomitant use of aliskiren with ACE inhibitors or angiotensin II receptor blockers (ARBs) in patients with diabetes mellitus (type 1 or type 2) and in patients with renal impairment (GFR <60 ml/min/1.73 m^2).
Anuria.

Warnings and precautions
Concomitant use of aliskiren with ACE inhibitors or angiotensin II receptor blockers (ARBs)
Hypotension, syncope, stroke, hyperkalaemia and deterioration of renal function (including acute renal failure) have occurred more frequently on dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren in combination with an ACE inhibitor or ARB. Combination of Rasilez HCT with an ACE inhibitor or ARB is therefore not recommended. In certain patients this combination is contraindicated (see "Contraindications").

Renal function/serum electrolyte changes
Use of Rasilez HCT may lead to worsening of renal function and a rise in serum potassium. This effect may be exacerbated by the concomitant use of agents such as ACE inhibitors, angiotensin II receptor blockers (ARBs) or NSAIDs, including COX2 inhibitors.
Patients with pre-existing renal disease, diabetes mellitus, hypovolaemia, heart failure or liver disease are particularly susceptible. Serum electrolytes and renal function should be closely monitored during treatment with Rasilez HCT.

Electrolytes
Potassium
Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazides should be administered with caution and regular monitoring of serum potassium in patients with conditions involving enhanced potassium loss.
Hypokalaemia should be corrected prior to the initiation of Rasilez HCT therapy. Coexisting hypomagnesaemia may make hypokalaemia more difficult to correct. As Rasilez HCT contains aliskiren, supplementation of potassium should be undertaken with great caution. Potassium and magnesium serum concentrations should be monitored regularly. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes.

Sodium
Thiazide diuretics can precipitate new onset hyponatraemia or exacerbate pre-existing hyponatraemia. This may be accompanied by neurological symptoms (vomiting, confusion, apathy). Thiazide diuretics should only be used after correction of any pre-existing hyponatraemia. Serum sodium concentrations should be monitored regularly.

Calcium
Thiazide diuretics decrease urinary calcium excretion and may cause elevation of serum calcium. Thiazide diuretics should only be started after correcting pre-existing hypercalcaemia or treating the condition responsible for it. Serum calcium concentrations should be monitored regularly.

Volume depletion
In severely volume-depleted patients, symptomatic hypotension may occur after initiation of therapy with Rasilez HCT. Existing volume depletion should be corrected before the start of treatment.

Anaphylactic reactions and angioedema
As with other medicinal products that act on the renin-angiotensin-aldosterone system (RAAS), hypersensitivity reactions such as anaphylactic reactions and angioedema – or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) – have also been reported in patients treated with aliskiren.
Some of the patients in question had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of medicines that can cause angioedema, including RAAS blockers (ACE inhibitors or angiotensin II receptor blockers). Anaphylactic reactions have been reported from post-marketing experience with unknown frequency (see "Adverse effects"). Special caution is necessary in patients with a predisposition for hypersensitivity. In controlled clinical studies, angioedema occurred rarely during treatment with aliskiren. The rate was similar to rates with placebo or hydrochlorothiazide.
Patients with a history of angioedema may be at increased risk of developing angioedema during treatment with aliskiren (see "Contraindications" and "Adverse effects"). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during, and especially at the start of, treatment (see "Adverse effects").
If angioedema, a hypersensitivity reaction or initial signs of either occur (in particular: difficulty breathing or swallowing; swelling of the face, extremities, eyes, lips and/or tongue), Rasilez HCT should be promptly discontinued and appropriate therapy and monitoring measures provided until complete and sustained resolution of signs and symptoms is achieved. Adrenaline should be administered if there is involvement of the tongue, glottis or larynx. In addition, measures should be taken to ensure a patent airway.

Renal impairment
No adjustment of the initial dose is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min). Due to the hydrochlorothiazide component, Rasilez HCT should be used with caution in patients with severe renal impairment (creatinine clearance <30ml/min).
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. Thiazide diuretics are ineffective as monotherapy in patients with severe kidney disease (creatinine clearance <30 ml/min) but may be useful in these patients when used with due caution in combination with a loop diuretic (see "Dosage / Administration" and "Properties / Actions").

Renal artery stenosis
No data are available on the use of Rasilez HCT in patients with unilateral or bilateral renal artery stenosis.
Other agents that act on the renin-angiotensin-aldosterone system (RAAS) may lead to deterioration of renal function in such patients. Particular caution should therefore be taken in these patients, and renal function closely monitored.

Hepatic impairment
No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, Rasilez HCT should be used with particular caution in patients with severe hepatic impairment (see "Dosage / Administration" and "Pharmacokinetics").

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Metabolic effects
Rasilez HCT may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia and precipitate gout in susceptible patients. Rasilez HCT is therefore not recommended for use in patients with hyperuricaemia and/or gout.

General
Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergies and asthma.
Rasilez HCT contains lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Concomitant use of ciclosporin A or itraconazole
Concomitant use of aliskiren with ciclosporin or itraconazole, potent P-glycoprotein inhibitors, is not recommended (see "Interactions").

Risk of acute myopia and secondary angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide contained in Rasilez HCT, can cause idiosyncratic reactions resulting in acute transient myopia or acute angle-closure glaucoma. This presents as acute onset of decreased visual acuity or ocular pain, which typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the drug as rapidly as possible. Surgical and medical measures may need to be considered if intraocular pressure cannot be controlled by other means. A pre-existing sulfonamide or penicillin allergy may be a risk factor for developing angle-closure glaucoma on treatment with hydrochlorothiazide.

Interactions
Aliskiren
Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX2) inhibitors
Concomitant administration of NSAIDs and COX2 inhibitors may attenuate the antihypertensive effect of Rasilez HCT. In patients who are elderly, volume depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs (or COX2 inhibitors) with Rasilez HCT may increase the risk of deterioration of renal function, including possible acute renal failure. These drugs should therefore be combined in such patients only with caution and monitoring of renal function.

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. This may lead to 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.

ACE inhibitors and angiotensin II receptor blockers (ARBs)
Coadministration of aliskiren with ACE inhibitors or ARBs is contraindicated in patients with diabetes mellitus (type 1 or type 2) and in patients with renal impairment (GFR <60 ml/min/1.73 m^2), and is not recommended in all other patients.

Potassium and potassium-sparing diuretics
Aliskiren administration may lead to increases in serum potassium. This risk may be increased by concomitant use of aliskiren with various substances, such as NSAIDs, including COX2 inhibitors, ACE inhibitors, ARBs, potassium-sparing diuretics and salt substitutes containing potassium.

Furosemide
When aliskiren was coadministered 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 therapy, and the dose of furosemide should be adjusted, if necessary, to avoid possible under-dosing.
The following substances have been investigated in clinical pharmacokinetic studies without clinically relevant interactions having been identified: acenocoumarol, atenolol, celecoxib, fenofibrate, pioglitazone, allopurinol, isosorbide-5-mononitrate, digoxin and hydrochlorothiazide. Therefore, no dose adjustment is necessary when these substances are coadministered.
Coadministration of aliskiren had no significant impact on the pharmacokinetics of atorvastatin, metformin or amlodipine. Therefore, no dose adjustment is necessary when these substances are coadministered. Concomitant administration of aliskiren with the following substances resulted in a 20-30% change in the C_{max} or AUC of aliskiren: 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 metabolized minimally by the cytochrome P450 enzymes, therefore aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolized by these enzymes.

P-glycoprotein interactions
In vitro studies indicate that MDR1 (Pgp) is the major efflux transporter involved in the absorption and disposition of aliskiren.

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

Moderate Pgp inhibitors
Coadministration 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 aliskiren and ketoconazole coadministration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Coadministration of a single dose of 300 mg aliskiren with 240 mg verapamil doubled the AUC and C_{max} of aliskiren. 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 ciclosporin A (200 and 600 mg) increases the C_{max} of 75 mg aliskiren approximately 2.5-fold and the AUC approximately 5-fold. In healthy subjects, itraconazole (100 mg) increased the AUC and C_{max} of aliskiren (150 mg) 6.5-fold and 5.8-fold, respectively. Concomitant use of these medicinal products and aliskiren is therefore not recommended (see Warnings and Precautions).

Hydrochlorothiazide
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides. There is no experience with concomitant use of aliskiren and hydrochlorothiazide with lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.

Other antihypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs).

Curare derivatives: Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

NSAIDs and Cox-2 selective inhibitors: Concomitant administration of NSAIDs (e.g. salicylic acid derivatives, indometacin) may diminish the diuretic and antihypertensive effects of the thiazide component of Rasilez HCT. Concurrent hypovolaemia may induce acute renal failure.

Medicinal products affecting serum potassium levels: The hypokalaemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics.

Medicinal products affecting serum sodium levels: The hyponatraemic effect of diuretics may be increased by concomitant administration of drugs such as antidepressants, antipsychotics or antiepileptics. Caution is advised in long-term administration of these drugs (see "Warnings and precautions").

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as adverse effects, favouring the onset of digitalis-induced cardiac arrhythmias.

Antidiabetic agents: It may be necessary to adjust the dosage of insulin and oral antidiabetic agents.

Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, prokinetic drugs such as cisapride may decrease the bioavailability of thiazide diuretics.

Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. Administration of hydrochlorothiazide and an ion exchange resin should thus be staggered, with as large a time interval as possible to minimize the interaction.
Vitamin D: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Calcium salts: Concomitant use of thiazide diuretics may lead to hypercalcaemia by increasing tubular calcium reabsorption.

Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, barbiturates or narcotics: Concomitant use of thiazide diuretics with alcohol, barbiturates or narcotics can potentiate orthostatic hypotension.

Pressor amines: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. However, the clinical significance of this effect is not sufficient to preclude their use.

Carbamazepine: Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Other interactions: Coadministration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic substances (e.g. cyclophosphamide, methotrexate) while potentiating their myelosuppressive effects.

Pregnancy / Lactation
Pregnancy
There are no adequate data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits. Other substances that act directly on the renin-angiotensin-aldosterone system (RAAS) have however been associated with serious fetal malformations and neonatal death. As for any medicine that acts directly on the RAAS, aliskiren must therefore not be used during pregnancy or by women planning to become pregnant. Healthcare professionals prescribing any RAAS-acting agents should counsel women of childbearing potential about the potential risk of these agents during pregnancy.
Hydrochlorothiazide crosses the placenta. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.
As no specific clinical studies have been performed with this combination, Rasilez HCT is contraindicated during pregnancy or in women planning to become pregnant (see "Contraindications"). If pregnancy is detected during therapy, Rasilez HCT must be discontinued as soon as possible.

Lactation
Rasilez HCT must not be used by women who are breast-feeding.
Hydrochlorothiazide is excreted into the breast milk. It is not known whether aliskiren is excreted in human milk. Aliskiren 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
The safety of Rasilez HCT has been evaluated in 9 clinical trials with more than 3900patients, including over 700 treated for 6 months, and 190 for over 1 year. The incidence of adverse events showed no association with gender, age, body mass index, race or ethnicity. Treatment with Rasilez HCT had an overall incidence of adverse effects at doses up to 300 mg/25 mg similar to placebo. Adverse events have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.
The most frequent adverse drug reaction with aliskiren/hydrochlorothiazide is diarrhoea.
Adverse effects are ranked according to frequency, including isolated reports.

Frequencies were defined as follows: *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 reports.* Within each frequency grouping, adverse effects are ranked in order of decreasing seriousness.

Gastrointestinal disorders
Common: Diarrhoea

Diarrhoea: Diarrhoea is a dose-dependent adverse effect of aliskiren. The incidence of diarrhoea was low in patients treated with Rasilez HCT in controlled clinical studies, and was not higher than in patients treated with aliskiren or hydrochlorothiazide.

Serum potassium: In a large, placebo-controlled clinical trial, the opposing effects of aliskiren (150 mg or 300 mg) and hydrochlorothiazide (12.5 mg or 25 mg) on serum potassium approximately balanced each other out in many patients. In other patients, one or the other effect may be dominant.
Serum potassium levels should be closely monitored.

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

Aliskiren
Immune system disorders
Rare: Hypersensitivity reactions.

Gastrointestinal disorders
Common: Diarrhoea.

Skin and subcutaneous tissue disorders
Uncommon: Rash, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Investigations
Common: Hyperkalaemia.

Renal and urinary disorders
Uncommon: Renal impairment.
Rare: Renal failure.

Nervous system disorders
Common: Dizziness/light-headedness.

Vascular disorders
Uncommon: Hypotension.

Angioedema has occurred during treatment with aliskiren. In controlled clinical studies, angioedema occurred rarely (0.3%) during treatment with aliskiren. The rate was similar to rates with placebo (0.4%) or hydrochlorothiazide (0.2%). 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 (frequency unknown). Some of the patients in question had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of medicines that can cause angioedema, including RAAS blockers (ACE inhibitors or angiotensin II receptor blockers). The incidence of cough was similar in patients given placebo (0.6%) and those given aliskiren (0.9%).
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 discontinued therapy because of anaemia. This effect is also seen with other agents acting on the renin-angiotensin-aldosterone system, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

Post-marketing experience
Frequency unknown: Anaphylactic reactions.
There have been cases of peripheral oedema and increased blood creatinine.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Rasilez HCT. The following adverse reactions have been reported in patients treated with thiazide diuretics, including hydrochlorothiazide, irrespective of their causal association with the medicinal product:
Very common: Hypokalaemia (mainly at higher doses), blood lipids increased.
Common: Urticaria and other forms of rash, decreased appetite, mild nausea and vomiting, orthostatic hypotension that may be aggravated by alcohol, anaesthetics or sedatives, impotence, hyponatraemia, hypomagnesaemia and hyperuricaemia.
Rare: Photosensitivity reaction, abdominal discomfort, constipation, diarrhoea, cholestasis or jaundice, arrhythmias, headache, dizziness, sleep disorder, depression, paraesthesia, visual impairment, thrombocytopenia, sometimes with purpura, hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state.
Very rare: Necrotizing vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leukopenia, agranulocytosis, bone-marrow failure, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

Post-marketing
Acute renal failure, renal disorder, aplastic anaemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute myopia and acute angle-closure glaucoma (frequency not known).

Overdosage
No data are available on overdose in humans. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aliskiren and hydrochlorothiazide. If symptomatic hypotension occurs, supportive treatment should be initiated.
In a study conducted in patients receiving haemodialysis, dialysis clearance of aliskiren was low (<2% of oral clearance). Dialysis is thus not suitable for treating an overdose of aliskiren.

Properties / Actions
ATC code: C09XA52

Rasilez HCT combines two antihypertensive compounds to control blood pressure in patients with essential hypertension. Aliskiren belongs to the class of direct renin inhibitors and hydrochlorothiazide belongs to the thiazide diuretics class of medicines.

Mechanism of action / Pharmacodynamics
Aliskiren
Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin. By inhibiting the enzyme renin, aliskiren inhibits the renin-angiotensin-aldosterone system (RAAS) by blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Substances that inhibit the RAAS (ACE inhibitors and angiotensin II receptor blockers) cause a compensatory rise in plasma renin activity (PRA). Treatment with aliskiren decreases PRA in hypertensive patients by 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. Elevated PRA is associated with increased cardiovascular risk in hypertensive and normotensive patients.
In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (including in the early morning) with a trough-to-peak ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximum blood-pressure-lowering effect was achieved after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment (12 months), and was independent of age, gender, body mass index and ethnicity.
There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. With cessation of treatment, blood pressure gradually returned to baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.
Combination therapy studies are available for aliskiren in combination with the diuretic hydrochlorothiazide, the ACE inhibitor ramipril, the calcium channel blocker amlodipine, the angiotensin receptor blocker valsartan, and the beta-blocker atenolol.
The 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 administration of ramipril. The differences in systolic and diastolic blood pressure were statistically significant. After 12 weeks, 46.3 % of patients in the group treated with aliskiren required add-on therapy with hydrochlorothiazide compared with 55.5 % of patients in the group treated with ramipril. After 22 weeks, 11.5 % of patients in the group treated with aliskiren required add-on therapy with amlodipine, compared with 15.7 % of patients in the group treated with ramipril. Tolerability was comparable in both treatment arms; however, coughing was reported more frequently with ramipril than with aliskiren (14.2 % vs. 4.4 %). The most frequent adverse event with aliskiren was diarrhoea (6.6 % vs. 5.0 % with ramipril).
Gastrointestinal safety and tolerability of 300 mg aliskiren and 10 mg ramipril were evaluated in a 54-week, 1:1 randomized, double-blind, multicentre, parallel-group, phase IV study in patients with essential hypertension at least 50 years of age. The aim of the study was to evaluate colon pathology, defined as a composite endpoint (hyperplastic polyps, inflammatory polyps, adenomatous polyps or carcinoma). A total of 1118 patients were enrolled. 578 of the 774 patients participating in the double-blind treatment phase underwent a second colonoscopy on its conclusion.
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. The number of patients with lesions at baseline was similar in the two groups (37.4% for aliskiren and 38.2% for ramipril). The relative risk of an abnormal finding in the aliskiren treatment group was less than 2 (RR = 1.03, p <0.0001), as compared with the ramipril treatment group.
The incidence of adverse events and serious adverse events was generally similar in both treatment groups. More patients developed a cough in the ramipril treatment group (12.0%) than in the aliskiren treatment group (3.7%). The incidence of diarrhoea was similar in the two treatment groups. Angioedema and angioedema-like events (including hand oedema) were more frequent with aliskiren than with ramipril. Particularly relevant colorectal events – including bloody diarrhoea (severe) and blood in the stool in two cases in the ramipril group and rectal/anal bleeding, or haematochezia, in the aliskiren group – were more frequent in the aliskiren group (2.1%) than in the ramipril group (0.5%).

Hydrochlorothiazide
Thiazide diuretics act primarily on the renal distal convoluted tubule. It has been shown that a high-affinity receptor exists in the renal cortex as the primary binding site for thiazide diuretics, and that NaCl transport is inhibited in the distal convoluted tubule. The mechanism of action of thiazide diuretics is through inhibition of this Na^+Cl^- symporter, perhaps by competing for the Cl^- site, thereby affecting the electrolyte reabsorption mechanism. Sodium and chloride excretion are increased to an approximately equal extent, and this diuretic action leads indirectly to a reduction in plasma volume, to increases in plasma renin activity and aldosterone secretion, to urinary potassium loss and to a decrease in serum potassium.

Clinical efficacy
Over 3900 hypertensive patients received Rasilez HCT once daily in clinical trials.
In hypertensive patients, once-daily administration of Rasilez HCT provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval. The antihypertensive effect is largely manifested within one week, and the maximum effect is generally seen within 4 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Upon withdrawal of aliskiren treatment (with or without hydrochlorothiazide), the return of blood pressure to baseline was gradual (3 to 4 weeks) with no evidence of a rebound effect.
Rasilez HCT was studied in a placebo-controlled trial in 2762 hypertensive patients with diastolic blood pressure ≥ 95 mmHg and < 110 mmHg (mean baseline blood pressure of 153.6/99.2 mmHg). In this study, Rasilez HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg produced dose-dependent blood pressure reductions (systolic/diastolic) from 17.6/11.9 mmHg to 21.2/14.3 mmHg, respectively, compared with 7.5/6.9 mmHg with placebo. The greater blood pressure reductions with these combination doses were also significantly larger than with the respective doses of aliskiren and hydrochlorothiazide when used alone. The combination of aliskiren and hydrochlorothiazide neutralized the reactive increase in PRA caused by hydrochlorothiazide.
When administered in a placebo-controlled trial as initial therapy in hypertensive patients unlikely to achieve blood pressure control with a single agent, Rasilez HCT in doses from 150 mg/12.5 mg to 300 mg/25 mg demonstrated significantly greater systolic/diastolic blood pressure control rates (<140/90 mmHg) compared to the respective monotherapies. In this population, Rasilez HCT 150 mg/12.5 mg to 300 mg/25 mg provided dose-dependent systolic/diastolic blood pressure reduction from 20.6/12.4 mmHg to 24.8/14.5 mmHg, which was significantly superior to the respective monotherapies. The safety of the combination therapy was similar to that of the respective monotherapies regardless of severity of hypertension or of the presence or absence of additional cardiovascular risk. Hypotension and related adverse effects were uncommon with the combination treatment, with no increased incidence in elderly patients.
In a study in 880 randomized patients not adequately responsive to 300 mg aliskiren treatment, the combination of 300 mg/25 mg aliskiren/hydrochlorothiazide produced systolic/diastolic blood pressure reductions of 15.8/11.0 mmHg, which were significantly greater than with 300 mg aliskiren monotherapy.
In a study in 722 randomized patients not adequately responsive to 25 mg hydrochlorothiazide treatment, the combination of 300 mg/25 mg aliskiren/hydrochlorothiazide produced systolic/diastolic blood pressure reductions of 16.7/10.7 mmHg, which were significantly greater than with 25 mg hydrochlorothiazide monotherapy.
In another clinical trial, the efficacy and safety of Rasilez HCT were also assessed in 489 obese hypertensive patients who did not respond to 25 mg hydrochlorothiazide (baseline systolic/diastolic blood pressure: 149.4/96.8 mmHg). In this difficult-to-treat population, Rasilez HCT provided a blood pressure reduction (systolic/diastolic) of 15.8/11.9 mmHg, compared with 15.4/11.3 mmHg for irbesartan/hydrochlorothiazide, 13.6/10.3 mmHg for amlodipine/hydrochlorothiazide and 8.6/7.9 mmHg for hydrochlorothiazide monotherapy, with safety similar to hydrochlorothiazide monotherapy.
In a study in 183 randomized patients with severe hypertension (mean diastolic blood pressure ≥ 105 mmHg and < 120 mmHg), an aliskiren treatment regimen with optional addition of hydrochlorothiazide was shown to be safe and efficacious in reducing blood pressure.
The double-blind, randomized ALTITUDE study evaluated aliskiren vs. placebo in N=8606 patients with type 2 diabetes mellitus and chronic renal impairment (albuminuria and/or GFR <60 ml/min/1.73 m^2). Approximately half the patients had previously known cardiovascular disease. Each patient's standard medication included either an ACE inhibitor or an angiotensin II receptor blocker (ARB). The primary endpoint was the incidence of cardiovascular or renal complications. Aliskiren was administered at a dose of 150 mg (first 4 study weeks) and 300 mg daily. The study was terminated early for lack of evidence that aliskiren was superior to placebo (HR 1.09, 95% CI 0.97-1.22). The data also indicated an increased incidence of renal complications (aliskiren: 4.7% vs. placebo: 3.3%), hyperkalaemia (36.9% vs. 27.1%), hypotension (18.4% vs. 14.6%) and stroke (2.7% vs. 2.0%).

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

Distribution
Aliskiren is evenly distributed systematically 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 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 (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). 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
Peak plasma concentrations (C_{max}) and exposure (AUC) of aliskiren increase linearly with increasing dose over the range of 75-600 mg.

Hydrochlorothiazide
The increase in mean AUC is linear and dose-proportional in the therapeutic range. There is no change in the pharmacokinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal with once-daily administration.

Absorption
Hydrochlorothiazide is rapidly absorbed following oral administration (T_{max} about 2 hours). The absolute bioavailability after oral administration is 70%. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasting state. The magnitude of these effects is small and has little clinical importance.

Distribution
The apparent volume of distribution is 4-8 litres/kg. Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Metabolism
Metabolism of hydrochlorothiazide is minimal.

Elimination
More than 95% of the absorbed dose is excreted as unchanged substance in the urine.
The elimination kinetics have been described as a bi-exponential decay function, with a terminal half-life of 6-15 hours.

Aliskiren / hydrochlorothiazide
Following oral administration of Rasilez HCT, median T_{max} is within 1 hour for aliskiren and within 2.5 hours for hydrochlorothiazide.
The extent of absorption of aliskiren and hydrochlorothiazide from Rasilez HCT is equivalent to the bioavailability of aliskiren and hydrochlorothiazide when administered as individual monotherapies. A similar food effect was observed for Rasilez HCT as for the individual monotherapies.

Pharmacokinetics in special patient populations
Patients with hepatic impairment
The pharmacokinetics of aliskiren and hydrochlorothiazide are not significantly affected in patients with mild to moderate liver disease. No data are available on patients with severe hepatic impairment treated with Rasilez HCT. However, due to the hydrochlorothiazide component, Rasilez HCT is contraindicated in patients with severe hepatic impairment (see "Contraindications").

Patients with renal impairment
The pharmacokinetics of aliskiren and hydrochlorothiazide are not significantly affected in patients with mild to moderate renal impairment. No data are available for Rasilez HCT in patients with severe renal impairment (creatinine clearance <30 ml/min).
In the presence of renal impairment, the mean C_{max} and AUC of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, the mean elimination half-life is almost doubled. The clearance of hydrochlorothiazide is reduced to a great extent compared with the renal clearance of around 300 ml/min in patients with normal renal function.
However, as expected for a substance which is cleared almost exclusively via the kidneys, renal function has a marked effect on the pharmacokinetics of hydrochlorothiazide. Rasilez HCT should therefore be used with particular caution in patients with severe renal impairment (creatinine clearance <30 ml/min; see "Contraindications" and "Warnings and precautions").
The pharmacokinetics of aliskiren were studied in dialysis patients with end stage renal disease (ESRD). Administration of a single oral dose of 300 mg aliskiren led to only very minor changes in the pharmacokinetics of aliskiren (increase in C_{max} of less than 1.2-fold; increase in AUC of up to 1.6 fold) compared to healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics in ESRD patients. Therefore, no dose adjustment is necessary in ESRD patients receiving haemodialysis.

Elderly patients
The pharmacokinetics of aliskiren and hydrochlorothiazide are not significantly affected in elderly patients. Limited data suggest that the systemic clearance of hydrochlorothiazide is slower in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

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

Preclinical data
Safety pharmacology studies with aliskiren did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings in toxicity studies in animals were attributable to the known irritation potential and the expected pharmacological effects of aliskiren. No carcinogenic potential was detected in a 2-year rat study and a 6-month transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant. The results of a subsequent 104-week oral toxicity study in marmoset monkeys showed an absence of any treatment-related histopathological changes in the gastrointestinal tract, but mild effects on the kidneys (including cortical artery hypertension, juxtaglomerular hyperplasia and increased renal extramedullary haematopoiesis) at doses of 10 and 20 mg/kg/day.
Aliskiren did not show mutagenic potential, embryofetal toxicity or teratogenicity. Fertility, prenatal development and postnatal development were unaffected in rats.
Preclinical evaluations to support the administration of hydrochlorothiazide in humans included *in vitro* genotoxicity assays and reproductive toxicity and carcinogenicity studies in rodents. Hydrochlorothiazide was not teratogenic and had no effects on fertility and conception. Extensive clinical data are available for hydrochlorothiazide and these are reflected in the relevant sections.
The aliskiren and hydrochlorothiazide combination was generally well tolerated by rats. There were no clinically relevant toxicological findings. The findings observed in the 2-week and 13-week toxicity studies were attributable to the pharmacological effects of the individual components.

Other information
Shelf life
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
October 2012

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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