

Rasilez HCT®

Composition

Active substances: Aiskiren (as aiskiren 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, iron oxide red (E 172), iron oxide yellow (E 172) 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 (E 172) 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 aiskiren and 12.5 mg hydrochlorothiazide

Rasilez HCT 150 mg/25 mg
Film-coated tablets containing 150 mg aiskiren and 25 mg hydrochlorothiazide

Rasilez HCT 300 mg/12.5 mg
Film-coated tablets containing 300 mg aiskiren and 12.5 mg hydrochlorothiazide

Rasilez HCT 300 mg/25 mg
Film-coated tablets containing 300 mg aiskiren 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 aiskiren 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 \geq 160 mmHg and/or diastolic blood pressure \geq 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 aiskiren 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 aiskiren/hydrochlorothiazide. Dosing should be individualized and adjusted according to the patient's clinical response.

Patients adequately treated with separate tablets of aiskiren and hydrochlorothiazide

Patients already receiving aiskiren 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 (\geq 160 mmHg and/or \geq 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 aiskiren/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 \geq 30 ml/min/1.73 m²; 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 m²; 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 aiskiren or hydrochlorothiazide, to sulphonamide derivatives or to any of the excipients of Rasilez HCT.

History of angioedema with aiskiren; hereditary or idiopathic angioedema.

Pregnancy and lactation (see "Pregnancy / Lactation").

Concomitant use of aiskiren with ACE inhibitors or angiotensin II receptor blockers (ARBs) in patients with diabetes mellitus (type I or type 2) and in patients with renal impairment (GFR $<$ 60 ml/min/1.73 m²).

Warnings and precautions

Concomitant use of aiskiren 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 aiskiren in combination with an ACE inhibitor or ARB. Combination of Rasilez HCT with an ACE inhibitor or ARB is therefore contraindicated. 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.

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 aiskiren 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

Aiskiren

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.

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 aiskiren approximately 2.5-fold and the AUC approximately 5-fold. In healthy subjects, itraconazole (100 mg) increased the AUC and C_{max} of aiskiren (150 mg) 6.5-fold and 5.8-fold, respectively. Concomitant use of these medicinal products and aiskiren is therefore not recommended (see Warnings and Precautions).

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.

Lactation

Rasilez HCT must not be used by women who are breast-feeding.

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 aiskiren and hydrochlorothiazide with lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.

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CYP450 interactions

Aiskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A) and does not induce CYP3A4. Aiskiren is metabolized minimally by the cytochrome P450 enzymes, therefore aiskiren 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 aiskiren.

Pgp substrates or weak inhibitors

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

Moderate Pgp inhibitors

Coadministration of ketoconazole (200 mg) with aiskiren (300 mg) resulted in an 80% increase in plasma levels of aiskiren (AUC and C_{max}). Preclinical studies indicate that aiskiren and ketoconazole coadministration enhances aiskiren gastrointestinal absorption and decreases biliary excretion. Coadministration of a single dose of 300 mg aiskiren with 240 mg verapamil doubled the AUC and C_{max} of aiskiren. The change in plasma levels of aiskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aiskiren were doubled; aiskiren doses of up to 600 mg, twice the highest recommended therapeutic dose, have been found to be well tolerated in controlled clinical trials. As a result, no dose adjustment for aiskiren is necessary.

Potent Pgp inhibitors

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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.

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 aiskiren in pregnant women. Aiskiren 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, aiskiren 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.

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The most frequent adverse drug reaction with aiskiren/hydrochlorothiazide is diarrhoea.

Adverse effects are ranked according to frequency, including isolated reports.

Frequencies were defined as follows: *Very common (\geq 1/10), common (\geq 1/100 to $<$ 1/10), uncommon (\geq 1/1000 to $<$ 1/100), rare (\geq 1/1000 to $<$ 1/10000), very rare ($<$ 1/10000), 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 aiskiren. 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 aiskiren or hydrochlorothiazide.

Post-marketing

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

Overdose

No data are available on overdose in humans. The most likely manifestation of overdose would be hypotension, related to the antihypertensive effect of aiskiren and hydrochlorothiazide. If symptomatic hypotension occurs, supportive treatment should be initiated.

In a study conducted in patients receiving haemodialysis, dialysis clearance of aiskiren was low ($<$ 2% of oral clearance). Dialysis is thus not suitable for treating an overdose of aiskiren.

Properties / Actions

ATC code: C09XA52

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

Mechanism of action / Pharmacodynamics

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 aiskiren. In controlled clinical studies, angioedema occurred rarely (0.3%) during treatment with aiskiren. The rate was similar to 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 aiskiren (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, olisthesia 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,