



New Zealand Data Sheet

APO-CILAZAPRIL/HCTZ

Cilazapril 5mg + hydrochlorothiazide 12.5mg tablet

Presentation

APO-CILAZAPRIL/HCTZ are pink, oval biconvex film-coated tablets. Each tablet is engraved "APO" on one side and "5", bisect "12.5" on the other side. Each tablet typically weighs 92mg.

Uses

Actions

APO-CILAZAPRIL/HCTZ is a combination of cilazapril (an angiotensin-converting enzyme inhibitor) and hydrochlorothiazide (a thiazide-diuretic agent). The antihypertensive effects of cilazapril and hydrochlorothiazide in the combination are additive resulting in a higher percentage of hypertensive patients responding satisfactorily than to either component administered alone. APO-CILAZAPRIL/HCTZ is highly effective in the treatment of hypertension and the effect is sustained for 24 hours.

Cilazapril is converted to its active metabolite, cilazaprilat, a specific long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and thereby induces a reduction of both sitting and standing systolic and diastolic blood pressure, usually with no change in heart rate and no orthostatic component.

Hydrochlorothiazide is a diuretic. The use of this agent increases plasma renin activity and aldosterone secretion resulting in a decrease in serum potassium. The cilazapril component, by blocking the angiotensin/aldosterone axis, attenuates the potassium loss associated with diuretic use. Although cilazapril alone is an antihypertensive, concomitant use with hydrochlorothiazide results in a greater reduction of blood pressure by complementary mechanisms.

Pharmacokinetics

Cilazapril is efficiently absorbed after oral administration of APO-CILAZAPRIL/HCTZ and rapidly converted by ester cleavage to the active form, cilazaprilat. The bioavailability of cilazaprilat from oral cilazapril approximates 60% based on urinary recovery data. Maximum plasma concentrations of cilazaprilat are consistently achieved within 2 hours. Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life, responsible for medicine accumulation, of about 9 hours.

Hydrochlorothiazide is rapidly absorbed following oral administration of APO-CILAZAPRIL/HCTZ. Maximum plasma concentrations are achieved within 2 hours post dosing. The bioavailability of hydrochlorothiazide after oral dose is about 65% based on urinary recovery. Hydrochlorothiazide is eliminated largely unchanged by the kidney, with a half-life of 7 to 11 hours.

AUC values increase proportionally for cilazaprilat and hydrochlorothiazide with increasing doses of cilazapril and hydrochlorothiazide in the combination dosage form. The pharmacokinetic parameters of cilazaprilat are not altered in the presence of increasing doses of the hydrochlorothiazide component. Concomitant administration of cilazapril with hydrochlorothiazide has no effect on the bioavailability of either cilazaprilat, cilazapril or hydrochlorothiazide. Administration of cilazapril and hydrochlorothiazide in the presence of food delays cilazaprilat T_{max} by 1.5 hours and reduces C_{max} by 24% and delays hydrochlorothiazide T_{max} by 1.4 hours and reduces C_{max} by 14% with no effect on overall bioavailability for both as assessed by AUC(0→24) value, indicating that there is an influence on rate but not on the extent of absorption.

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Indications

APO-CILAZAPRIL/HCTZ is indicated for the treatment of patients with hypertension who are not adequately controlled on monotherapy.

Dosage and Administration

Standard Dosage for Adults

The dosage of APO-CILAZAPRIL/HCTZ is one tablet administered once daily. As food intake has no clinically significant influence on absorption, APO-CILAZAPRIL/HCTZ can be administered before or after meals. The dose should always be taken at about the same time of day.

Special Dosage Instructions

Renal insufficiency

When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic rather than a thiazide diuretic is preferred for use with cilazapril; therefore, for patients with severe renal dysfunction, APO-CILAZAPRIL/HCTZ is not recommended. (See Precautions, haemodialysis/anaphylaxis.)

Prior diuretic therapy

In patients who are currently being treated with a diuretic for a reason other than hypertension, symptomatic hypotension occasionally can occur following the initial dose of cilazapril. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued for 2 to 3 days prior to beginning therapy with cilazapril. If discontinuation of the diuretic is not possible, patients should be supervised for several hours after dosing, until blood pressure stabilises.

Elderly

In clinical studies the efficacy and tolerability of cilazapril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Children

Safety and efficacy in children have not been established; therefore APO-CILAZAPRIL/HCTZ is not recommended for administration to children.

Contraindications

APO-CILAZAPRIL/HCTZ is contraindicated in patients who are hypersensitive to cilazapril or other ACE inhibitors, to thiazides or to other sulphonamide-derived medicines, in patients with a history of angioneurotic oedema related to previous treatment with an ACE inhibitor and in patients with anuria.

APO-CILAZAPRIL/HCTZ is contraindicated in pregnancy. ACE inhibitors pass through the placenta and can be presumed to cause disturbances in the foetus-blood pressure-regulating mechanisms. Oligohydramnios, as well as hypotension and oliguria/anuria in newborns have been reported. Isolated cases of defects in skull ossification have been described. Given during pregnancy they have been reported to entail prematurity and low birth weight.

Warnings and Precautions

General

APO-CILAZAPRIL/HCTZ should not be used in patients with aortic stenosis or outflow tract obstruction.

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Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia

Neutropenia has been rarely reported with cilazapril and hydrochlorothiazide combination therapy. Periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease and renal disease.

Renal impairment

Inhibition of the renin-angiotensin-aldosterone system may be anticipated to lead to changes in renal function in susceptible individuals. In patients whose renal function depends primarily on the activity of the renin-angiotensin-aldosterone system, such as patients with severe heart failure or with unilateral or bilateral renal artery stenosis, treatment with ACE inhibitors including APO-CILAZAPRIL/HCTZ may produce increases in blood urea nitrogen and/or serum creatinine. Although these alterations are usually reversible upon discontinuation of APO-CILAZAPRIL/HCTZ and/or diuretic therapy, cases of severe renal dysfunction and, rarely, acute renal failure have been reported (see Undesirable Effects).

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when cilazapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Should this occur during therapy with APO-CILAZAPRIL/HCTZ discontinuation of therapy may be required.

Evaluation of the hypertensive patient should always include an assessment of renal function.

Hepatic impairment

APO-CILAZAPRIL/HCTZ should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Patients with impaired liver function should be monitored closely.

Haemodialysis/anaphylaxis

Although the mechanism involved has not been definitely established, there is clinical evidence that haemodialysis with polyacrylonitrile methallyl sulfate high-flux membranes (e.g. AN69), haemofiltration or LDL-apheresis, if performed in patients being treated with ACE inhibitors, including cilazapril, can lead to the provocation of anaphylaxis/anaphylactoid reactions including life-threatening shock. The above-mentioned procedures must therefore be avoided in such patients.

Furthermore, anaphylactic reactions can occur in patients undergoing desensitisation therapy with wasp or bee venom while receiving an ACE inhibitor. Cilazapril must therefore be interrupted before the start of desensitisation therapy. Additionally, in this situation, cilazapril must not be replaced by a beta blocker.

Serum potassium

The hypokalaemic effect of hydrochlorothiazide is usually attenuated by the effect of cilazapril.

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In clinical trials, hyperkalaemia was rarely seen in patients using cilazapril and hydrochlorothiazide combination therapy. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with APO-CILAZAPRIL/HCTZ. Frequent monitoring of serum potassium may be advisable if these risk factors are present.

Lithium

Lithium should generally not be given with ACE inhibitors and diuretics. ACE inhibitors and diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Surgery/anaesthesia

In patients undergoing major surgery or being anaesthetised with agents that produce hypotension, APO-CILAZAPRIL/HCTZ may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be treated with volume expanders.

Metabolic and endocrine effects

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium levels in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hyperuricaemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

Hyperglycaemia may occur with thiazide diuretics in diabetic patients. Dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Diabetes

Administration of ACE inhibitors in patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycaemic agents or insulin.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema has been reported in patients being treated with angiotensin-converting enzyme inhibitors as well as with cilazapril and hydrochlorothiazide combination therapy.

If angioneurotic oedema of the extremities, face, lips, tongue, glottis and/or larynx, occurs, treatment with APO-CILAZAPRIL/HCTZ should be immediately discontinued. The patient should be closely observed until swelling disappears. Angioneurotic oedema associated with laryngeal oedema may be fatal. If there is involvement of either the tongue, glottis, or larynx which could precipitate an upper airway obstruction, appropriate therapy should be instituted. Angioneurotic oedema involving other anatomical sites generally resolves without treatment, though antihistamines have been found to be of benefit in relieving symptoms.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma with the use of thiazides.

Use in Pregnancy and Lactation

Category D

APO-CILAZAPRIL/HCTZ is contraindicated in pregnancy (see Contraindications).

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It is not known whether cilazaprilat passes into human breast milk but studies in rats indicate the presence of cilazaprilat in rat maternal milk at concentrations resembling those in plasma. Hydrochlorothiazide passes into human breast milk. If the use of APO-CILAZAPRIL/HCTZ is deemed essential to the mother, the patient should stop breast-feeding.

Adverse Effects

APO-CILAZAPRIL/HCTZ is usually well tolerated. In most cases, side effects are transient, mild or moderate in degree, and do not require discontinuation of therapy. In clinical trials with cilazapril and hydrochlorothiazide combination therapy, no side effects peculiar to this combination have been observed. Side effects occurring in patients ($\geq 2\%$) include headache, dizziness, fatigue and cough. As with other ACE inhibitors, angioneurotic oedema has been reported, although rarely in patients taking cilazapril (see Precautions).

As for other ACE inhibitors, isolated cases of pancreatitis, in some cases fatal, have been reported in patients treated with cilazapril and hydrochlorothiazide combination therapy.

Isolated cases of acute renal failure have been reported in patients with severe heart failure, renal artery stenosis or renal disorders (see Precautions).

Single cases of liver function disorders, such as increased liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis, have been reported.

Laboratory Test Findings

Clinically important changes in standard laboratory tests have rarely been associated with cilazapril and hydrochlorothiazide combination therapy. Scattered incidence of neutropenia/leukopenia, elevated liver enzymes and decreased serum sodium have been reported. However, in controlled clinical trials, a lower overall incidence of clinically relevant laboratory abnormalities were observed with cilazapril and hydrochlorothiazide combination therapy compared to placebo. None of the cilazapril and hydrochlorothiazide combination therapy treated patients discontinued because of laboratory abnormalities.

Interactions

In some patients non-steroidal anti-inflammatory medicines may reduce the antihypertensive effects of concomitantly administered APO-CILAZAPRIL/HCTZ.

Overdosage

No specific information is available on the treatment of overdosage with APO-CILAZAPRIL/HCTZ. Therapy with APO-CILAZAPRIL/HCTZ should be discontinued and the patient observed closely. In the event of an overdose, symptomatic and supportive measures should be employed. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures. Both cilazapril and cilazaprilat are poorly removed by haemodialysis. Haemodialysis is more effective during the first few hours after dosing, when plasma levels of unbound substances are highest.

Pharmaceutical Precautions

Shelf life 2 years from the date of Manufacture

Store at or below 25°C

Protect from heat, light and moisture.



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Medicine Classification

Prescription only medicine

Package Quantities

APO-CILAZAPRIL/HCTZ 5mg/12.5mg is packed in bottles of 100 tablets.

Further Information

APO-CILAZAPRIL/HCTZ contains corn starch.

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