



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

1. PRODUCT NAME

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE – cilazapril 5mg and hydrochlorothiazide 12.5mg film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cilazapril monohydrate 5.22mg (equivalent to Cilazapril 5mg) and Hydrochlorothiazide 12.5mg

Excipient(s) with known effect

HYDROCHLOROTHIAZIDE contains sulphur.

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is lactose free and gluten free.

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE contains Red Ferric Oxide (orange shade # 34690).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Standard Dosage

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

Special Populations

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/hydrochlorothiazide; therefore, for patients with severe renal dysfunction (creatinine

clearance <10ml/min), APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is not recommended. (See section 4.4 Special warnings and precautions for use, haemodialysis/anaphylaxis.)

Liver cirrhosis

No pharmacokinetic studies have been performed with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE in patients with liver cirrhosis. As significant hypotension may occur in patients with liver cirrhosis treated with standard doses of ACE inhibitors, caution should be exercised in the unlikely event that patients with liver cirrhosis require treatment with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE.

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 APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE. 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. Although pharmacokinetic data shows that clearance of both components in elderly patients was reduced, this had no therapeutic consequences (see section 5.2 Pharmacokinetics in special populations, elderly patients). Therefore, no dose adjustment is recommended.

Paediatric Population

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

Maximum Tolerated Daily Dose

The maximum tolerated daily dose of APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is one tablet administered once daily.

4.3 Contraindications

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is contraindicated in patients with known hypersensitivity to cilazapril or other ACE inhibitors, to thiazides or to other sulphonamide-derived medicines.

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is contraindicated in patients with a history of angioedema associated with previous ACE inhibitor therapy and with hereditary or idiopathic angioedema.



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is contraindicated in patients with anuria.

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is contraindicated during pregnancy and lactation (see section 4.6 Fertility, pregnancy and lactation, Pregnancy and Breast-feeding).

Concomitant use of APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE and aliskiren in patients with diabetes mellitus or renal impairment ($GFR < 60 \text{ ml/min/1.73m}^2$) is contraindicated.

4.4 Special warnings and precautions for use

Aortic stenosis/hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patients with obstructive cardiac disorders (e.g. mitral stenosis, aortic stenosis, hypertrophic cardiomyopathy), since cardiac output cannot increase to compensate for systemic vasodilation and there is a risk of severe hypotension.

Hypotension

Patients should start treatment with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE only after they have been stabilised on each component given at the same dose as in the combined product. ACE inhibitors may cause severe hypotension, especially when starting treatment. First-dose hypotension is most likely to occur in patients whose renin-angiotensin-aldosterone system is activated, such as in renovascular hypertension or other causes or renal hypoperfusion, sodium or volume depletion, or previous treatment with other vasodilators. These conditions can co-exist, particularly in severe heart failure.

Hypotension should be treated by placing the patient supine and volume expansion. APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE may be continued once the patient is volume replete but should be given a lower dose or discontinued if hypotension persists.

At-risk patients should start treatment with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE under medical supervision, with a low initial dose and careful titration.

Similar caution should be taken for patients with angina pectoris or cerebrovascular disease, in whom hypotension can cause myocardial or cerebral ischaemia.

Concomitant therapy with Aliskiren

Concomitant use of ACE inhibitors with aliskiren is not recommended due to dual blockade of the renin-angiotensin-aldosterone system and reports of hypotension, syncope, stroke, hyperkalaemia and changes in renal function (including acute renal failure) in susceptible individuals (see section 4.3 Contraindications)

Hepatic disorders

Cases of liver function disorders, such as increased values of liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis have been reported. Patients who develop jaundice or marked elevations of hepatic enzymes should discontinue APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE and receive appropriate medical follow-up (see section 4.4 Special warnings and precautions for use – Hepatic impairment).

Blood disorders

Thrombocytopenia, neutropenia and agranulocytosis have been associated with both ACE inhibitors and thiazides. Agranulocytosis has been especially reported in patients with renal failure or collagen vascular disease and those receiving immunosuppressive therapy. Periodic monitoring of leukocyte count is recommended in such patients. Autoimmune hemolytic anemia has been reported with thiazides.

Renal impairment

Inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors may lead to changes in renal function in patients whose renal function depends primarily on the activity of the renin-angiotensin-aldosterone system and produce increases in blood urea nitrogen and/or serum creatinine. Although these alterations are usually reversible upon discontinuation of ACE inhibitor and/or diuretic therapy, cases of severe renal dysfunction and rarely, acute renal failure have been reported (see section 4.8 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, with cilazapril and hydrochlorothiazide. Should this occur discontinuation of therapy with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE may be required.

Evaluation of the hypertensive patient should always include an assessment of renal function. When treated with cilazapril, patients with renal artery stenosis have an increased risk of renal insufficiency, including acute renal failure. Therefore, caution should be exercised in these patients. In the patient population described above, renal function should be monitored during the first weeks of therapy. If renal failure occurs, treatment should be discontinued

Hepatic impairment

Since minor alterations of fluid and electrolyte balance may precipitate encephalopathy, APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE must be used with caution in patients with impaired hepatic function or progressive liver disease. Liver function should be monitored closely. In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE should be initiated with great caution because significant hypotension may occur. In patients with ascites, APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is not recommended.



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

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.

Desensitisation: Anaphylactic reactions can occur in patients undergoing desensitisation therapy with wasp or bee venom while receiving an ACE inhibitor. APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE must be stopped before the start of desensitisation therapy and should not be replaced by a beta blocker.

Serum electrolytes

ACE inhibitors can cause hyperkalaemia due to suppression of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), hyperkalemia can occur.

Thiazides increase potassium excretion and can cause hypokalemia. Hypokalemia may also occur in patients receiving APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE, although to a lesser extent than that seen in patients receiving thiazide monotherapy. In patients receiving combination therapy of cilazapril/hydrochlorothiazide the hypokalemic effect of hydrochlorothiazide is usually attenuated by the effect of cilazapril. In reported 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/HYDROCHLOROTHIAZIDE. Frequent monitoring of serum potassium may be advisable if these risk factors are present.

Thiazides may also cause hyponatraemia and dehydration. The risk of hyponatraemia is greater in women, patients with hypokalaemia or low sodium/solute intake and in the elderly.

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.

Electrolytes and renal function should be monitored in patients receiving APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE.

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

Anaesthetic agents with blood pressure lowering effects can cause hypotension in patients receiving ACE inhibitors. Hypotension in this setting can be corrected with volume expansion.

Other Metabolic disorders

Hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients. Thiazides may increase serum uric acid levels and precipitate acute gout. APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE should be used with caution in patients with a history of gout.

Diabetes

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

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. Glucose levels should be carefully monitored during initiation of treatment with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE.

Hypersensitivity/angioneurotic oedema

Angioedema has been associated with ACE inhibitors (including cilazapril/hydrochlorothiazide combination therapy) with a reported incidence of 0.1 – 0.5%. Angioedema due to ACE inhibitors can present as recurrent episodes of facial swelling, which resolves on withdrawal, or as acute oropharyngeal oedema and airways obstruction which requires emergency treatment and may be life-threatening. A variant form is angioedema of the intestine, which tends to occur within the first 24-48 hours of treatment. The risk of angioedema appears to be greater in black-skinned patients than in non-black-skinned patients. Patients with a history of angioedema unrelated to ACE inhibitors may be at greater risk (see section 4.3 Contraindications). Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma with the use of thiazides.

Ethnicity

ACE inhibitors are less effective as antihypertensives in black-skinned patients of African descent. These patients also have a higher risk of angioedema.

Dual blockade of the renin-angiotensin-aldosterone system

Although not specifically studied in clinical trials, adding an angiotensin-receptor antagonist to APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is not recommended. This recommendation is based on reported clinical trials investigating the combination of an ACE inhibitor other than cilazapril and an angiotensin receptor antagonist which elicit only

marginal incremental drop in blood pressure as compared to monotherapy. As a consequence of inhibiting the renin-angiotensin-aldosterone system an increased risk of developing adverse events was observed in susceptible individuals, including worsening of renal failure, hypotension and hyperkalaemia. Based on these results dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an angiotensin-receptor antagonist to cilazapril) is not recommended. If still considered necessary, it should be limited to individually defined cases with close monitoring of renal function.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.

Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventative measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8 Undesirable effects)

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetics Interactions

Interactions mainly related to cilazapril

Aliskiren

The combination of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment ($GFR < 60 \text{ ml/min/1.73m}^2$) and is not recommended in all patients (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use – Hypotension)

Lithium

Reversible increases in serum lithium concentrations have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of cilazapril and hydrochlorothiazide combination with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

Other antihypertensive agents

An additive effect may be observed when cilazapril is administered in combination with other blood pressure-lowering agents.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with cilazapril and hydrochlorothiazide combination therapy. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium impairment (see section 5.1 Pharmacodynamic Properties - Mechanism of Action and section 4.4 Special warnings and precautions for use). Therefore, the combination of cilazapril and hydrochlorothiazide combination therapy with the above-mentioned drugs is not recommended (see section 4.4 Special warnings and precautions for use). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with cilazapril and hydrochlorothiazide combination (see section 4.4 Special warnings and precautions for use). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of cilazapril and hydrochlorothiazide combination therapy.

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics

Concomitant use of anaesthetic medicinal products applied during the course of general anaesthesia, as well as tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4 Special warnings and precautions for use).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥3g/day

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Vildagliptin, Sirolimus and Everolimus

Patients taking concomitant DPP-IV inhibitor (e.g. vildagliptin) or mTOR inhibitor (e.g. everolimus, sirolimus) therapy may be at increased risk for angioedema. Caution should be used when starting a DPP-IV inhibitor or mTOR inhibitor in a patient already taking an ACE inhibitor.

Other Drugs

There was no increase in digoxin plasma concentrations when cilazapril was administered concomitantly with digoxin. No clinically significant drug interactions were observed when cilazapril was administered concomitantly with nitrates, coumarin anticoagulants and H₂-receptor blockers. No significant pharmacokinetic drug interaction between cilazapril and furosemide or thiazides were noted.

Interactions mainly related to hydrochlorothiazide

Digoxin

Since thiazide-induced hypokalaemia may occur during therapy with cilazapril and hydrochlorothiazide combination, which may increase the risk of arrhythmia associated with digoxin therapy, monitoring of potassium plasma levels is advised.

Medicinal products that could induce torsades de pointes

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when a patient is simultaneously being treated with medicinal products that could induce torsades de pointes such as:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, defetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, trifluoperazine, sulpiride, tiapride, haloperidol, droperidol)
- Other medicinal products (e.g. bepridil, cisapride, diphemanil, halofantrine, ketanserine, pentamidine, terfenadine)

Non-depolarizing muscle relaxants

Non-depolarizing muscle relaxants should not be administered simultaneously, due to possible intensification and prolongation of the muscular relaxing effect.

Calcium salts and vitamin D

Simultaneous administration of hydrochlorothiazide together with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Cholestyramine/colestipol

Cholestyramine and colestipol reduce the absorption of hydrochlorothiazide.

Anticholinergics

Concomitant use of anticholinergics (e.g. atropine, biperiden) may increase the bioavailability of hydrochlorothiazide due to reduced gastrointestinal mobility and decreased gastric emptying.

Amantidine

Simultaneous administration of amantidine and hydrochlorothiazide may increase possible adverse effects of amantadine.

Cytotoxic drugs (e.g. methotrexate, cyclophosphamide)

Simultaneous administration of hydrochlorothiazide and cytotoxic drugs may decrease the elimination of the cytotoxic drug and consequently increase the risk of developing myelodepression.

Iodine containing contrast media

In case of dehydration induced by hydrochlorothiazide, there is an increased risk of acute renal impairment, in particular when larger doses of iodine containing contrast media are administered.

Cyclosporine

Simultaneous administration of cyclosporine and hydrochlorothiazide may increase the risk of developing hyperuricaemia and gout-like complications.

Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracyclines.

Pharmacodynamic Interactions

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE can be taken with or without food.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE is contraindicated in pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE during pregnancy (see section 4.3 Contraindications).

Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly, spina bifida) and also an increased risk of kidney malformations.

Exposure to ACE inhibitors therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3 Preclinical safety data – Teratogenicity). Should exposure to ACE inhibitors occur from the second trimester of pregnancy, ultrasound examination of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

There is limited experience with hydrochlorothiazide during pregnancy. Thiazides cross the placenta and may be associated with neonatal jaundice, thrombocytopenia and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion.

Breast-feeding

Hydrochlorothiazide passes into human breast milk. APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE must not be administered to nursing mothers and alternative treatments with better established safety profiles during breastfeeding are preferable (see section 4.3 Contraindications)

Animal data show the presence of cilazaprilat in rat milk. However, no information is available regarding the safety of cilazapril during breast feeding in humans.

Fertility

Cilazapril had no effect on male or female fertility in rats. Pre-clinical studies on the effect on peri- and postnatal performance and on fertility were not conducted with the combination.

4.7 Effects on ability to drive and use machines

Occasionally dizziness and fatigue may occur, especially when starting therapy (see section 4.8 Undesirable Effects – Post Marketing)

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

4.8 Undesirable effects

Post Marketing

The following adverse reactions have been reported in association with cilazapril and/or other ACE inhibitors alone, hydrochlorothiazide and/or other thiazide-type diuretics alone, and in those receiving combined therapy.

Frequency categories are as follows¹:

Very common $\geq 1/10$

Common $\geq 1/100$ and $< 1/10$

Uncommon $< 1/100$

¹Estimates of frequency are based on the proportion of patients reporting each adverse reaction during cilazapril and hydrochlorothiazide combination therapy reported clinical trials that included a total combined population of 1 097 patients. Adverse reactions that were not observed during cilazapril and hydrochlorothiazide combination therapy clinical trials but have been reported in association with monotherapy with either component or with other ACE inhibitors or thiazide diuretics, or derived from post-marketing case reports, are classified as 'uncommon' ($<1/100$). The category 'uncommon' incorporates 'rare' ($\geq 1/10\ 000$ and $<1/1\ 000$) and 'very rare' ($<1/10\ 000$).

The frequency of adverse reactions attributable to cilazapril, occurring in patients receiving combination therapy (cilazapril+ hydrochlorothiazide), may differ from that seen in patients receiving cilazapril monotherapy. Reasons may include (i) differences between the target populations treated with cilazapril and hydrochlorothiazide combination and cilazapril, (ii) differences in cilazapril dose, and (iii) specific effects of combination therapy.

Adverse reactions to cilazapril

Blood and lymphatic disorders

Uncommon: Neutropenia, agranulocytosis, thrombocytopenia, anaemia

Cardiac disorders

Uncommon: Myocardial infarction, tachycardia, palpitations, angina pectoris

Vascular disorders

Common: Dizziness

Uncommon: Hypotension

Gastrointestinal disorders

Common: Nausea

Uncommon: Pancreatitis

Hepatobiliary disorders

Uncommon: Abnormal liver function test (including transaminases, bilirubin, alkaline phosphatase, gamma GT), cholestatic hepatitis with or without necrosis

Immune system disorders

Uncommon: Angioedema (may involve the face, lips, tongue, glottis, larynx or gastrointestinal tract), anaphylaxis, lupus-like syndrome (symptoms may include vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies, increased erythrocyte sedimentation rate, eosinophilia and leukocytosis)

Nervous system disorders

Common: Headache

Uncommon: Dysgeusia, transient ischaemic attack, ischaemic stroke

Skin and subcutaneous tissue disorders

Uncommon: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pseudoporphyria, pemphigus, bullous pemphigoid, exfoliative dermatitis, psoriaform dermatitis, psoriasis (exacerbation), lichen planus, urticarial, vasculitis photosensitivity reactions, rash, alopecia, onycholysis.

Renal and urinary disorders

Uncommon: Renal impairment, acute renal failure, blood creatinine increased, blood urea increased, hyperkalaemia, hyponatraemia

Respiratory, thoracic and mediastinal disorders

Uncommon: Acute interstitial pneumonitis, acute pulmonary oedema

General disorders and administration site conditions

Common: Fatigue

Adverse reactions to hydrochlorothiazide

Blood and lymphatic system disorders

Uncommon: Thrombocytopaenia, haemolytic anaemia, granulocytopenia

Cardiac disorders

Uncommon: Arrhythmia

Eye disorders

Uncommon: Lacrimation decreased, visual impairment

Gastrointestinal disorders

Common: Nausea

Uncommon: Dry mouth, sialoadenitis, loss of appetite

General disorders and administration site conditions

Common: Fatigue

Hepatobiliary disorders

Uncommon: Cholestatic jaundice

Immune system disorders

Uncommon: Hypersensitivity (angioedema, anaphylaxis)

Metabolism and nutrition disorders

Uncommon: Hypokalaemia, hyponatraemia, hypochloraemia, hypomagnesaemia, hypercalcaemia, hypocalciuria, hypovolaemia/dehydration, metabolic alkalosis, hyperglycaemia, hyperuricaemia, gout, hypercholesterolaemia (increased total, LDL and VLDL cholesterol) hypertriglyceridaemia

Musculoskeletal and connective tissue disorders

Uncommon: Muscle cramp

Nervous system disorders

Common: Dizziness

Psychiatric disorders

Uncommon: Sleep disorder, depression

Renal and urinary disorders

Uncommon: Interstitial nephritis, renal impairment

Reproductive system and breast disorders

Uncommon: Sexual dysfunction

Respiratory, thoracic and mediastinal disorders

Uncommon: Acute interstitial pneumonitis, acute pulmonary oedema

Skin and subcutaneous tissue disorders

Uncommon: Rash, photosensitivity, pseudoporphyria, cutaneous vasculitis

Vascular disorders

Uncommon: Hypotension

Description of selected adverse events

Hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see Section 4.4 Special warnings and precautions for use). Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.

Renal impairment and acute renal failure are more likely in patients with severe heart failure, renal artery stenosis, pre-existing renal disorders or volume depletion. The events of transient ischaemic attack and ischaemic stroke reported rarely in association with ACE inhibitors may be related to hypotension in patients with underlying cerebrovascular disease. Similarly, myocardial ischaemia may be related to hypotension in patients with underlying ischaemic heart disease. Hypokalaemia may occur in patients receiving cilazapril and hydrochlorothiazide combination therapy, although less commonly than in patients receiving thiazide monotherapy.

The risk of hyponatraemia is greater in women, patients with hypokalaemia or low sodium/solute intake, and the elderly.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent associate between HCTZ and NMSC has been observed (see also sections 4.4 Special warning and precautions for use and section 5.1 Pharmacodynamic properties).

Laboratory abnormalities

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 reported 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Limited data is available for overdosage with APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE in humans.

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. In predisposed patients (e.g. prostatic hyperplasia) hydrochlorothiazide overdose may induce acute urinary retention.

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. If indicated, cilazaprilat, the active form of cilazapril, may be removed from the general circulation by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group

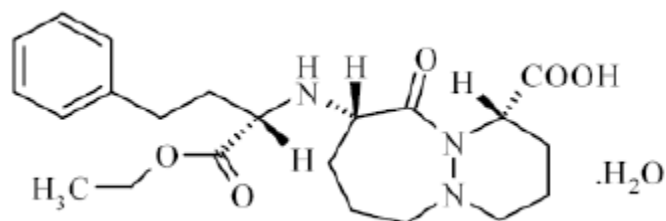
Angiotensin-converting enzyme (ACE) Inhibitor and diuretic

ATC code

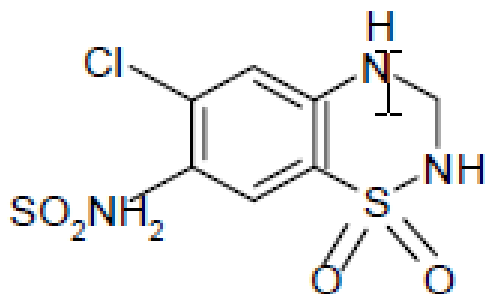
C09BA08

Chemical Structure:

Cilazapril



Hydrochlorothiazide



Mechanism of action

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE 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/HYDROCHLOROTHIAZIDE 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 the conversion of the inactive angiotensin I to angiotensin II (a potent vasoconstrictor).



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

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. Concomitant use of cilazapril with hydrochlorothiazide results in a greater reduction of blood pressure by complementary mechanisms.

Clinical efficacy and safety

Reported studies performed with cilazapril and hydrochlorothiazide combination therapy have demonstrated that the combination of cilazapril and hydrochlorothiazide administered once daily at various doses statistically and clinically reduce systolic and diastolic blood pressure compared to placebo 24 hours after dosing. The combination at various doses produced a statistically and clinically significant greater blood pressure reduction than either of the two individual components. In patients not responding to 5mg cilazapril given as monotherapy, the addition of hydrochlorothiazide at a low dose of 12.5mg once daily substantially improved the response treatment. The combination is effective irrespective of age, gender and ethnicity.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4 Special warning and precautions for use)

5.2 Pharmacokinetic properties

Absorption

Cilazapril is efficiently absorbed after oral administration of cilazapril and hydrochlorothiazide combination therapy. The bioavailability of cilazaprilat from oral cilazapril approximates 60% based on urinary recovery data.

Hydrochlorothiazide is rapidly absorbed following oral administration of cilazapril and hydrochlorothiazide combination therapy. The bioavailability of hydrochlorothiazide after oral dose is about 65% based on urinary recovery.

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 $AUC(0 \rightarrow 24)$ value, indicating that there is an influence on rate but not on the extent of absorption.

Distribution

Cilazapril is rapidly converted by ester cleavage to the active form, cilazaprilat.

Biotransformation

Maximum plasma concentrations of cilazaprilat are consistently achieved within 2 hours.

Hydrochlorothiazide maximum plasma concentrations are achieved within 2 hours post dosing.

Elimination

Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of about 9 hours.

Hydrochlorothiazide is eliminated largely unchanged by the kidney, with a half-life of 7 to 11 hours.

Pharmacokinetics in special populations

Renal impairment

In patients with renal impairment, higher plasma concentrations of cilazaprilat are observed than in patients with normal renal function, since drug clearance is reduced when creatinine clearance is lower. Cilazaprilat is not eliminated in patients with complete renal failure, but haemodialysis reduces concentrations of both cilazapril and cilazaprilat to a limited extent.

Elderly patients

In elderly patients whose renal function is normal for their age, plasma concentrations of cilazaprilat may be up to 40% higher and clearance 20% lower, than in younger patients.

Hepatic impairment

In patients with liver cirrhosis increased plasma concentrations and reduced plasma and renal clearance were observed, with a greater effect on cilazapril than on its active metabolite cilazaprilat.

5.3 Preclinical safety data

The acute oral toxicity of cilazapril is low. The mean lethal doses in rats, mice and cynomolgus monkeys were higher than 2000mg/kg body weight. The acute oral toxicity of cilazapril in mice was not enhanced by the combination of hydrochlorothiazide.

As with other ACE inhibitors, the kidney was the primary target of systemic toxicity in subchronic and chronic toxicity studies with cilazapril alone. The findings included increased plasma urea and creatinine values and thickening of the glomerular arterioles, occasionally in association with hyperplasia of the juxtaglomerular cells. These changes were demonstrated to be reversible and are a consequence of exaggerated pharmacodynamic activity of cilazapril occurring only at high multiples of the therapeutic human doses i.e. 40-fold or more of the maximum recommended human dose of 5mg. Subchronic and chronic toxicity studies with hydrochlorothiazide in rats and dogs showed no noticeable findings except for changes in the electrolyte balance (hypokalaemia). Combination studies with cilazapril and hydrochlorothiazide caused similar findings as observed with cilazapril alone. The main combination effects were the attenuation of thiazide induced potassium loss and decreased motoric activity at high doses in monkeys.

Carcinogenicity

There was no evidence of carcinogenicity of cilazapril and no relevant findings with hydrochlorothiazide in mice and rats. No tests of carcinogenicity were conducted with the combination.

Mutagenicity

Cilazapril did not show any mutagenic or genotoxic effect in various mutagenicity tests, performed in vitro and in vivo. The combination of cilazapril and hydrochlorothiazide caused no relevant signs of a mutagenic potential for the case of therapeutic treatment.

Impaired fertility

Cilazapril had no effect on male or female fertility in rats. Pre-clinical studies on the effect on peri- and postnatal performance and on fertility were not conducted with the combination.

Teratogenicity

Cilazapril was not teratogenic in rats and cynomolgus monkeys. As with other ACE inhibitors, signs of foetotoxicity were observed in rats. The main findings were increased pre-implantation loss and fewer viable foetuses. They occurred only at 50mg/kg corresponding to high multiples of therapeutic human doses, i.e. 500-fold or more of the maximum recommended human dose of 5mg. A slightly higher incidence of pelvic dilation was observed in rats at 7mg/kg/day.

There was no evidence of teratogenicity with the combination of cilazapril and hydrochlorothiazide in rats and mice.



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline Cellulose
- Maize starch (corn starch)
- Sodium Stearyl fumarate
- Hyprollose (Hydroxypropyl Cellulose)
- Hypromellose (Hydroxypropyl Methyl Cellulose)
- Macrogol 8000 (Polyethylene Glycol 8000)
- Titanium Dioxide
- Iron oxide red (Red Ferric Oxide orange shade # 34690).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 2 years from the date of manufacture

6.4 Special precautions for storage

Store at or below 25°C

Protect from heat light and moisture.

6.5 Nature and contents of container

APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE 5mg/12.5mg: HDPE bottles containing 100 tablets

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.

32 Hillside Road

Wairau Valley

AUCKLAND 0627



APO-CILAZAPRIL/HYDROCHLOROTHIAZIDE

Telephone: (09) 444 2073

Fax: (09) 444 2951

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

03 September 2009

10. DATE OF REVISION OF THE TEXT

21 January 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Interactions mostly related to Cilazapril – information regarding Vildagliptin, Sirolimus and Everolimus added