Data Sheet

Inhibace Plus®

Cilazapril 5 mg + hydrochlorothiazide 12.5 mg tablet

Antihypertensive; ACE inhibitor and diuretic

Composition

Active ingredients

Cilazapril and hydrochlorothiazide.

Each tablet contains 5 mg cilazapril and 12.5 mg hydrochlorothiazide.

Excipients

Lactose monohydrate, maize starch, hypromellose, purified talc, sodium stearyl fumarate, titanium dioxide, red iron oxide. (See Warnings and precautions for a warning concerning lactose.)

Appearance

Inhibace Plus tablets are oval, biconvex, scored, reddish-brown to brown tablets that are approximately 11.7 mm in length and 6.2 mm in width.

Properties and Effects

Mechanism of action

Inhibace Plus 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. Inhibace Plus 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).

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 studies

Studies performed with Inhibace Plus have demonstrated that the combination of cilazapril and hydrochlorothiazide administered once daily at various doses statistically and clinically reduced

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 5 mg cilazapril given as monotherapy, the addition of hydrochlorothiazide at a low dose of 12.5 mg once daily substantially improved the response to treatment. The combination is effective irrespective of age, gender and ethnicity.

Pharmacokinetics

Cilazapril is efficiently absorbed after oral administration of Inhibace Plus 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 of about 9 hours.

Hydrochlorothiazide is rapidly absorbed following oral administration of Inhibace Plus. 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.

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.

Indications

Inhibace Plus is indicated for the treatment of patients with hypertension who are not adequately controlled on monotherapy.

Dosage and Administration

Standard dosage

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

Special dosage instructions

Patients with renal impairment

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, Inhibace Plus is not recommended. (See Warnings and precautions - *Haemodialysis/anaphylaxis*.)

Liver cirrhosis

No pharmacokinetic studies have been performed with Inhibace Plus 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 Inhibace Plus.

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 patients

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 Inhibace Plus is not recommended for administration to children.

Contraindications

Inhibace Plus 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.

Inhibace Plus is contraindicated during pregnancy and lactation (see Warnings and precautions - *Pregnancy, nursing mothers*).

Warnings and precautions

General

Inhibace Plus should not be used in patients with aortic stenosis or outflow tract obstruction.

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 (see Warnings and precautions – *Hepatic impairment*).

Neutropenia

Neutropenia and agranulocytosis have been rarely reported with ACE inhibitors. Periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease and renal disease such as systemic lupus erythematosus and scleroderma, or in patients receiving immunosuppressive therapy, especially when they also have impaired renal function.

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 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 Inhibace Plus. Should this occur, discontinuation of therapy with Inhibace Plus may be required.

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

Hepatic impairment

Since minor alterations of fluid and electrolyte balance may precipitate hepatic coma, Inhibace Plus must be used with caution in patients with impaired hepatic function or progressive liver disease. Liver function should be monitored closely.

Haemodialysis/anaphylaxis

Although the mechanism involved has not been definitely established, there is clinical evidence that haemodialysis with polyacrylonitrite 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Serum potassium

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

In clinical trials, hyperkalaemia was rarely seen in patients using Inhibace Plus. 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 Inhibace Plus. Frequent monitoring of serum potassium may be advisable if these risk factors are present.

Surgery/anaesthesia

The use of ACE inhibitors in combination with anaesthetic drugs in surgery that also have blood pressure lowering effects can produce arterial hypotension. If this occurs, volume expansion by means of intravenous infusion or if resistant to these measures - angiotensin II infusion is indicated.

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.

Hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Diabetes

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

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.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema has been reported in patients being treated with angiotensin-converting enzyme inhibitors including Inhibace Plus.

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

Dual blockade of the renin-angiotensin-aldosterone system

Although not specifically studied in clinical trials, adding an angiotensin-receptor antagonist to Inhibace Plus is not recommended. This recommendation is based on clinical trials investigating the combination of an ACE inhibitor other than cilazapril and an angiotensin receptor antagonist which elicited only a 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.

Ability to drive and use machines

As with other ACE-inhibitors, impairment of performance in activities requiring complete mental alertness (e.g. driving a motor vehicle) is not to be expected with Inhibace Plus. However, it should be noted that dizziness may occasionally occur (see Undesirable Effects - *Post Marketing*).

Pregnancy, nursing mothers

Although there is no specific experience with Inhibace Plus, use of ACE inhibitors in human pregnancy has been associated with oligohydramnios, intrauterine growth restriction, neonatal hypotension, anuria and renal tubular dysplasia. Foetotoxicity has been observed with ACE inhibitors in animals.

In addition, foetal exposure to ACE inhibitors during the first trimester of pregnancy has been 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.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion.

Pregnant women should be informed of the potential hazards to the foetus and must not take Inhibace Plus during pregnancy (see Contraindications).

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. Inhibace Plus must not be administered to nursing mothers (see Contraindications).

Undesirable Effects

In clinical trials with Inhibace Plus, no side effects peculiar to this combination have been observed. Side effects occurring in patients (≥ 2%) include headache, dizziness, fatigue and cough.

Post Marketing

Inhibace Plus is usually well tolerated. In most cases, side effects are transient, mild or moderate in degree, and do not require discontinuation of therapy.

Blood and lymphatic disorders: Blood disorders have been reported with ACE Inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia and anaemia.

Cardiac disorders: Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patient with heart failure and in sodium- or volume-depleted patients. Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations and chest pain.

Gastrointestinal disorders: Isolated cases of pancreatitis, in some cases fatal, have been reported with ACE inhibitors including Inhibace Plus.

Hepatobiliary disorders: 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.

Immune system disorders: As with other ACE inhibitors, angioneurotic oedema has been reported, although rarely in patients taking cilazapril (see Warnings and precautions - Neutropenia). Since this syndrome can be associated with laryngeal oedema, Inhibace Plus should be discontinued and appropriate therapy instituted without delay when involvement of the face, lips, tongue, glottis and/or larynx occurs.

Skin and subcutaneous tissue disorders: Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur with ACE inhibitors; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported. Photosensitivity reactions are among the most frequently reported skin reactions in patients taking thiazides. Other reported skin reactions include vasculitis, erythema multiforme and pseudoporphyria.

Renal and urinary disorders: Isolated cases of acute renal failure have been reported in patients with severe heart failure, renal artery stenosis or renal disorders (see Warnings and precautions – Renal impairment).

Respiratory, thoracic and mediastinal disorders: Acute interstitial pneumonitis and acute pulmonary oedema are rare but potentially dangerous complications in patients receiving thiazides and may be due to a hypersensitivity reaction.

Laboratory abnormalities

Clinically important changes in standard laboratory tests have rarely been associated with Inhibace Plus. 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 Inhibace Plus compared to placebo. None of the Inhibace Plus treated patients discontinued because of laboratory abnormalities.

Interactions

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.

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

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

As with other ACE inhibitors, use of Inhibace Plus concomitantly with a non-steroidal anti-inflammatory drug (NSAID) may diminish the antihypertensive effect of Inhibace Plus.

Overdosage

No specific information is available on the treatment of overdosage with Inhibace Plus. The most likely manifestations are hypotension, which may be severe, hyperkalaemia, hyponatraemia and renal impairment with metabolic acidosis. Treatment should be mainly symptomatic and supportive. If indicated, cilazaprilat, the active form of Inhibace Plus, can be partially removed from the body by haemodialysis. Specific therapy with angiotensinamide may be considered if conventional therapy is ineffective.

Stability

Store below 25 °C.
This medicine should not be used after the expiry date shown on the pack.
Keep out of reach of children.

Medicine Classification

Prescription medicine

Packs

Inhibace Plus Tablets (scored) 5mg/12.5mg, packs of 28

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