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, pale red 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\(_{\text{max}}\) by 1.5 hours and reduces C\(_{\text{max}}\) by 24% and delays hydrochlorothiazide T\(_{\text{max}}\) by 1.4 hours and reduces C\(_{\text{max}}\) 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.

**Pre-clinical Safety**

The acute oral toxicity of cilazapril is low. The mean lethal doses in rats, mice, and cynomolgus monkeys were higher than 2000 mg/kg body weight. The acute oral toxicity of cilazapril in mice was not enhanced by the combination with 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 5 mg. 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.

**Impairment of 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 50 mg/kg corresponding to high multiples of therapeutic human doses, i.e. 500-fold or more of the maximum recommended human dose of 5 mg. A slightly higher incidence of pelvic dilation was observed in rats at 7 mg/kg/day. There was no evidence of teratogenicity with the combination of cilazapril and hydrochlorothiazide in rats and mice.

**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 Inhibace Plus; therefore, for patients with severe renal dysfunction (creatinine clearance <10 mL/min), 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 Inhibace Plus. 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. Although pharmacokinetic data shows that clearance of both components in elderly patients was reduced, this had no therapeutic consequence (see Pharmacokinetics in Special Populations). Therefore no dose adjustment is recommended.

**Children**
Safety and efficacy in children have not been established; therefore Inhibace Plus is not recommended for administration to children.

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**Contraindications**

Inhibace Plus is contraindicated in patients with known hypersensitivity to cilazapril or other ACE inhibitors, to thiazides or to other sulphonamide-derived medicines. Inhibace Plus is contraindicated in patients with a history of angioedema associated with previous ACE inhibitor therapy and with hereditary or idiopathic angioedema. Inhibace Plus is contraindicated in patients with anuria.

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

Concomitant use of Inhibace Plus and aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²) is contraindicated (see Interactions).
Warnings and precautions

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 Inhibace Plus only after they have been stabilized 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 of 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. Inhibace Plus may be continued once the patient is volume replete, or discontinued if hypotension persists.

At-risk patients should start treatment with Inhibace Plus under medical supervision.

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

Dual blockade of the Renin-Angiotensin-Aldosterone-System (RAAS)
The concomitant use of ACE inhibitors with Angiotensin II Receptor Blockers (ARBs) or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of the RAAS is therefore not recommended (see Contraindications and Interactions). If dual blockade therapy of ACE inhibitors with ARBs is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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 Inhibace Plus and receive appropriate medical follow-up (see Warnings and precautions – 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 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. When treated with Inhibace Plus, 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 populations as 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 hepatic encephalopathy, Inhibace Plus 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, Inhibace Plus should be initiated with great caution because significant hypotension may occur. In patients with ascites, Inhibace Plus is not recommended.

**Serum electrolytes**

ACE inhibitors can cause hyperkalemia 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 hypokalaemia. Hypokalaemia may also occur in patients receiving Inhibace Plus, although to a lesser extent than that seen in patients receiving thiazide monotherapy. In patients receiving Inhibace Plus 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.

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 Inhibace Plus.

**Diabetes**

Administration of ACE inhibitors to 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 Inhibace Plus.

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 may precipitate acute gout. Inhibace Plus should be used with caution in patients with a history of gout.

Hypersensitivity/Angioedema
Angioedema has been associated with ACE inhibitors (including Inhibace Plus), 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 Contraindications). Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma with the use of thiazides.

Concomitant use of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors or dipeptidyl peptidase IV (DPP-IV) inhibitors may lead to an increased risk for angioedema. Caution should be used when using mTOR inhibitors or DPP-IV inhibitors concomitantly with ACE inhibitors (see Interactions).

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. Desensitization: Anaphylactic reactions can occur in patients undergoing desensitisation therapy with wasp or bee venom while receiving an ACE inhibitor. Inhibace Plus must be stopped before the start of desensitization therapy, and should not be replaced by a beta blocker.

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.

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

Lactose intolerance
The formulation contains lactose monohydrate. Therefore, patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Ability to drive and use machines
Occasionally dizziness and fatigue may occur, especially when starting therapy (see Undesirable Effects - Post Marketing).

Pregnancy, nursing mothers
The use of Inhibace Plus is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take Inhibace Plus during pregnancy (see 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 Inhibace Plus 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 inhibitor 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 Pre-clinical Safety - Teratogenicity). Should exposure to ACE inhibitor have occurred 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.

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. Hydrochlorothiazide passes into human breast milk. Inhibace Plus must not be administered to nursing mothers and alternative treatments with better established safety profiles during breastfeeding are preferable (see Contraindications).

Undesirable Effects

Post Marketing
The following adverse reactions have been seen 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 follows:\(^1\):

Very common  \( \geq 1/10 \)
Common          \( \geq 1/100 \) and < 1/10
Uncommon        < 1/100

**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, psoriasiform dermatitis, psoriasis (exacerbation), lichen planus, urticarial, vasculitis photosensitivity reactions, rash, alopecia, onycholysis

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\(^1\) Estimates of frequency are based on the proportion of patients reporting each adverse reaction during Inhibace Plus clinical trials that included a total combined population of 1’097 patients. Adverse reactions that were not observed during Inhibace Plus 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/’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 Inhibace Plus and Inhibace, (ii) differences in cilazapril dose, and (iii) specific effects of combination therapy.
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
**Description of selected adverse events**

Hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see Warnings and Precautions). 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 Inhibace Plus, 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.

**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**

**Interactions mainly related to cilazapril**

**Dual blockade of the Renin-Angiotensin-Aldosterone-System (RAAS)**

Clinical trial data has shown that dual blockade of the RAAS through the concomitant use of ACE inhibitors with angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. Dual blockage of the RAAS is therefore not recommended (see Contraindications and Warnings and Precautions). If dual blockade
therapy of ACE inhibitors with ARBs is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

The combination of ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m²) and is not recommended in all other patients (see Contraindications and Warnings and Precautions – Hypotension).

**Lithium**

Reversible increases in serum lithium concentrations have been reported during concomitant administration of lithun 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 Inhibace Plus with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

**Other antihypertensive agents**

An additive effect may be observed when Inhibace Plus 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 Inhibace Plus. 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 Mechanism of Action and Warnings and Precautions). Therefore, the combination of Inhibace Plus with the above-mentioned drugs is not recommended (see Warnings and Precautions). 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 Inhibace Plus (see Warnings and Precautions). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake.

**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 Warnings and Precautions).

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

When ACE inhibitors are administered simultaneously with non-steroidal antiinflammatory 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.
**mTOR inhibitors**
Concomitant use of ACE inhibitors with mTOR inhibitors may lead to an increased risk for angioedema (see Warnings and Precautions – Hypersensitivity/Angioedema).

**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.

Concomitant use of ACE inhibitors with DPP-IV inhibitors may lead to an increased risk for angioedema (see Warnings and Precautions - Hypersensitivity/Angioedema).

**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.

**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 Inhibace Plus, 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 hypokalemia, 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 amantidine.

**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 hyperuricemia and gout-like complications.

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

### Overdosage

Limited data is available for overdosage with Inhibace Plus 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.

### 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.
**Disposal of Medicines**

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established ‘collection systems’ if available in your location.

**Medicine Classification**

Prescription medicine

**Packs**

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

**Name and Address**

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**Date of Preparation**

9 December 2014