

Summary of Product Characteristics

1. Name of the medicinal product

HYPERIL tablets 5 mg

HYPERIL tablets 10 mg

HYPERIL tablets 20 mg

2. Qualitative and quantitative composition

Each HYPERIL 5 mg tablet contains HYPERIL dihydrate equivalent to 5 mg anhydrous HYPERIL.

Each HYPERIL 10 mg tablet contains HYPERIL dihydrate equivalent to 10 mg anhydrous HYPERIL.

Each HYPERIL 20 mg tablet contains HYPERIL dihydrate equivalent to 20 mg anhydrous HYPERIL.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Tablets.

4. Clinical particulars

4.1 Therapeutic indications

Hypertension

Treatment of hypertension.

Heart Failure

Treatment of symptomatic heart failure.

Acute Myocardial Infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal Complications of Diabetes Mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

HYPERIL can be used alone or in combination with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

HYPERIL tablets should be administered orally in a single daily dose. As with all other medication taken once daily, HYPERIL tablets should be taken at approximately the same time each day. The absorption of HYPERIL tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure response (see section 4.4)

Hypertension

HYPERIL tablets may be used as monotherapy or in combination with other classes of antihypertensive therapy (see sections 4.3, 4.4, 4.5 and 5.1).

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

The usual effective maintenance dosage is 20 mg administered in a single daily dose. In general if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased. The maximum dose used in long-term, controlled clinical trials was 80 mg/day.

Diuretic-Treated Patients

Symptomatic hypotension may occur following initiation of therapy with HYPERIL tablets. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with HYPERIL tablets. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with HYPERIL tablets should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of HYPERIL tablets should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage Adjustment In Renal Impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below.

Table 1 Dosage adjustment in renal impairment.

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Use in Hypertensive Paediatric Patients aged 6-16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see section 5.1).

In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Heart Failure

In patients with symptomatic heart failure, HYPERIL tablets should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. HYPERIL tablets may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of HYPERIL tablets should be increased:

- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35 mg once daily.

Dose adjustment should be based on the clinical response of individual patients.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with HYPERIL tablets. Renal function and serum potassium should be monitored (see section 4.4).

Posology in Acute Myocardial Infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with HYPERIL tablets.

Starting dose (first 3 days after infarction)

Treatment with HYPERIL tablets may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of HYPERIL tablets is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial HYPERIL tablets dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) HYPERIL tablets should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with HYPERIL tablets (see section 4.2).

Renal Complications of Diabetes Mellitus

In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg HYPERIL tablets once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial HYPERIL tablets dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric population

There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications (see section 5.1). HYPERIL is not recommended in children in other indications than hypertension.

HYPERIL is not recommended in children below the age of 6, or in children with severe renal impairment (GFR <30ml/min/1.73m²) (see section 5.2).

Elderly

In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 should be used to determine the starting dose of HYPERIL tablets. Thereafter, the dosage should be adjusted according to the blood pressure response.

Use in kidney transplant patients

There is no experience regarding the administration of HYPERIL tablets in patients with recent kidney transplantation. Treatment with HYPERIL tablets is therefore not recommended.

4.3 Contraindications

- Hypersensitivity to HYPERIL tablets, to any of the excipients listed in section 6.1 or any other angiotensin converting enzyme (ACE) inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- In combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR < 60 ml/min/1.73m² (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Symptomatic Hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving HYPERIL tablets, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with HYPERIL tablets. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of HYPERIL tablets may be necessary.

Hypotension In Acute Myocardial Infarction

Treatment with HYPERIL tablets must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then HYPERIL tablets should be withdrawn.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, HYPERIL tablets should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal Function Impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial HYPERIL tablets dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of HYPERIL tablets therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when HYPERIL tablets has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or HYPERIL tablets may be required.

In acute myocardial infarction, treatment with HYPERIL tablets should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with HYPERIL tablets (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of HYPERIL tablets.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including HYPERIL tablets. This may occur at any time during therapy. In such cases, HYPERIL tablets should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patient's airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Anaphylactoid reactions in Haemodialysis Patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

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

Neutropenia/ Agranulocytosis

Neutropenia/ Agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. HYPERIL tablets should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If HYPERIL tablets are used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy."

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, HYPERIL tablets may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, HYPERIL tablets may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including HYPERIL tablets. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulfamethoxazole also known as cotrimoxazole). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium

The combination of lithium and HYPERIL tablets is generally not recommended (see section 4.5).

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensive agents

When HYPERIL tablets is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, 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 (see sections 4.3, 4.4 and 5.1).

Drugs that may increase the risk of angioedema

Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema.

Diuretics

When a diuretic is added to the therapy of a patient receiving HYPERIL tablets the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when HYPERIL tablets is added. The possibility of symptomatic hypotension with HYPERIL tablets can be minimised by discontinuing the diuretic prior to initiation of treatment with HYPERIL tablets (see section 4.2 and section 4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

Monitoring of potassium should be undertaken as appropriate. See section 4.4. If HYPERIL is given with a potassiumlosing diuretic, diuretic induced hypokalaemia may be ameliorated.

Lithium

Reversible increases in serum lithium concentrations and toxicity 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 lithium toxicity with ACE inhibitors. Use of HYPERIL tablets with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid $\geq 3g/day$

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. These effects are usually reversible. 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.

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Tricyclic antidepressants / Antipsychotics / Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, 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.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk of hyperkalaemia (see section 4.4).

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

HYPERIL tablets may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra indicated during the second and third trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

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 section 5.3.). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding Because no information is available regarding the use of HYPERIL tablet during breastfeeding, HYPERIL tablet is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with HYPERIL tablets and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease

Immune system disorders

not known: anaphylactic/anaphylactoid reaction

Endocrine Disorders

rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

very rare: hypoglycaemia

Nervous system and psychiatric disorders:

common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations.
rare: mental confusion, olfactory disturbance
Not known: depressive symptoms, syncope.

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

common: cough
uncommon: rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion
rare: dry mouth
very rare: pancreatitis, intestinal angioedema, hepatitis- either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:

uncommon: rash, pruritus
rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis
very rare: sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:

common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Reproductive system and breast disorders:

uncommon: impotence
rare gynaecomastia

General disorders and administration site conditions:

uncommon: fatigue, asthenia

Investigations:

uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia.

Safety data from clinical studies suggest that HYPERIL is generally well tolerated in hypertensive paediatric patients, and that the safety profile in this age group is comparable to that seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Limited data are available for overdose 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.

The recommended treatment of overdose is intravenous infusion of normal saline 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. If ingestion is recent, take measures aimed at eliminating HYPERIL tablets (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). HYPERIL tablets may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03

Mechanism of Action

HYPERIL tablets is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Pharmacodynamic effects

Whilst the mechanism through which HYPERIL lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, HYPERIL is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of HYPERIL remains to be elucidated.

Clinical efficacy and safety

The effect of HYPERIL tablets on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose HYPERIL tablets produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation ($p = 0.002$) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation ($p = 0.036$) compared with low dose. Risk reductions for all-cause mortality (8%; $p = 0.128$) and cardiovascular mortality (10%; $p = 0.073$) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% ($p=0.002$) in patients treated with high-dose HYPERIL tablets compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of HYPERIL tablets.

The results of the study showed that the overall adverse event profiles for patients treated with high or low dose HYPERIL tablets were similar in both nature and number. Predictable events resulting from ACE

inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose HYPERIL tablets compared with low dose.

In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of HYPERIL tablets and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394, patients who were administered the treatment within 24 hours of an acute myocardial infarction, HYPERIL tablets produced a statistically significant risk reduction in mortality of 11% versus control (2p=0.03). The risk reduction with glyceryl trinitrate was not significant but the combination of HYPERIL tablets and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p=0.02). In the sub-groups of elderly (age > 70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with HYPERIL tablets or HYPERIL tablets plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for HYPERIL tablets. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with HYPERIL tablets treatment but these were not associated with a proportional increase in mortality.

In a double-blind, randomised, multicentre trial which compared HYPERIL tablets with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, HYPERIL tablets 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with HYPERIL tablets showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of HYPERIL tablets reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.

HYPERIL treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA_{1c}).

Renin-angiotensin system (RAS)-acting agents

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

In a clinical study involving 115 paediatric patients with hypertension, aged 6-16 years, patients who weighed less than 50 kg received either 0.625 mg, 2.5 mg or 20 mg of HYPERIL once a day, and patients who weighed 50 kg or more received either 1.25 mg, 5 mg or 40 mg of HYPERIL once a day. At the end of 2 weeks, HYPERIL administered once daily lowered trough blood pressure in a dose-dependent manner with a consistent antihypertensive efficacy demonstrated at doses greater than 1.25 mg.

This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mm Hg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of HYPERIL. The dose-dependent antihypertensive effect of HYPERIL was consistent across several demographic subgroups: age, Tanner stage, gender, and race.

5.2 Pharmacokinetic properties

HYPERIL is an orally active non-sulphydryl-containing ACE inhibitor.

Absorption

Following oral administration of HYPERIL, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of HYPERIL is approximately 25% with inter-patient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. HYPERIL absorption is not affected by the presence of food.

Distribution

HYPERIL does not appear to be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE). Studies in rats indicate that HYPERIL crosses the blood-brain barrier poorly.

Elimination

HYPERIL does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing HYPERIL has an effective half-life of accumulation of 12.6 hours. The clearance of HYPERIL in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in HYPERIL absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

Renal impairment

Impaired renal function decreases elimination of HYPERIL, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min).

HYPERIL can be removed by dialysis. During 4 hours of haemodialysis, plasma HYPERIL concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

Heart failure

Patients with heart failure have a greater exposure of HYPERIL when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of HYPERIL, there is reduced absorption of approximately 16% compared to healthy subjects.

Paediatric population

The pharmacokinetic profile of HYPERIL was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73m². After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of HYPERIL occurred within 6 hours, and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults.

AUC and C_{max} values in children in this study were consistent with those observed in adults.

Elderly

Elderly have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. Pharmaceutical particulars

6.1 List of excipients

HYPERIL, tablets 5 mg

Other ingredients: Mannitol, colloidal silicon dioxide, calcium hydrogen phosphate dihydrate, pregelatinized corn starch, microcrystalline cellulose, titanium dioxide (E171), iron oxide red (E172), magnesium stearate.

HYPERIL, tablets 10 mg

Other ingredients: Mannitol, colloidal silicon dioxide, calcium hydrogen phosphate dihydrate, pregelatinized corn starch, microcrystalline cellulose, titanium dioxide (E171), quinoline yellow (E104), magnesium stearate.

HYPERIL, tablets 20 mg

Other ingredients: Mannitol, colloidal silicon dioxide, calcium hydrogen phosphate dihydrate, pregelatinized corn starch, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

30 (3x10) 5 mg tablets of HYPERIL in blister packs, in a box.

30 (3x10) 10 mg tablet of HYPERIL in a blister packs, in a box.

30 (3x10) 20 mg HYPERIL tablet in blister packs, in a box.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75 300 Lukavac
Bosnia and Herzegovina

8. Marketing authorisation number(s)

HYPERIL,30 tablets 5 mg, Number: 04-07.3-2-4868/15

HYPERIL, 30 tablets 10 mg, Number: 04-07.3-2-4869/15

HYPERIL, 30 tablets 20 mg, Number: 04-07.3-2-4870/15

9. Date of renewal of the authorization:

09.09.2015.

10. Date of revision of the text

20/02/2018