**For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory**

# LISTRIL PLUS

## 1. GENERIC NAME

Lisinopril and Hydrochlorothiazide Tablets

## 2. QUALITATIVE & QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Lisinopril I.P equivalent to

Lisinopril anhydrous ….5 mg

Hydrochlorothiazide I.P. …..12.5mg

The excipients are Disodium hydrogen ortho phosphate, Magnesium stearate, Talc Pregelatinized starch, Mannitol, Starch

## 3. DOSAGE FORM AND STRENGTH

Dosage form: Uncoated tablets
Strength: 5 mg + 12.5 mg

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

The management mild moderate hypertension in patients who have been stabilized on the individual components given in the same proportions.

### 4.2 Posology and method of administration

**Primary Hypertension**

The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, Listril Plus should be taken at approximately the same time each day.

In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

**Renal impairment**

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency).

Listril Plus is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, Listril Plus may be used, but only after titration of the individual components. The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

**Prior Diuretic Therapy**

Symptomatic hypotension may occur following the initial dose of Listril Plus; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Listril Plus. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

**Elderly**

No adjustment of dosage is required in the elderly.

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

Lisinopril, within a daily dosage range of 20 to 80 mg, was equally effective in the elderly (65 years or over) and non-elderly hypersensitive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

**Paediatric population**

The safety and efficacy in children have not been established.

## 4.3 Contraindications

- Hypersensitivity to lisinopril, hydrochlorthiazide or to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor
- Hypersensitivity to any sulphonamide-derived drugs.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Anuria.
- Severe hepatic impairment.
- The concomitant use of Listril Plus with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

## 4.4 Special warnings and precautions for use

**Non-melanoma skin cancer**

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

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

**Symptomatic hypotension**

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients, but 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-dependant hypertension. Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. In patients at increased risk of symptomatic hypotension, initiation of therapy

and dose adjustment should be monitored under close medical supervision. Particular consideration applies to patients with ischaemic heart or cerebrovascular disease, because 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 for further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

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

**Aortic and mitral valve stenosis / hypertrophic cardiomyopathy**

As with other ACE inhibitors, lisinopril 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.

**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.

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.

**Renal function impairment**

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (corresponds to moderate or severe renal insufficiency).

Lisinopril/hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance less than or equal to 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

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 stenosis of the artery to a solitary kidney, who have been treated with ACE 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, renal function should be monitored during the first few weeks of lisinopril/hydrochlorothiazide therapy.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril 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 lisinopril may be required.

**Prior diuretic therapy**

The diuretic therapy should be discontinued for 2-3 days prior to initiation with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

**Renal transplantation**

Should not be used, since there is no experience with patients recently transplanted with a kidney.

**Anaphylactoid reactions in haemodialytic patients**

The use of lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low- density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

**Anaphylactoid reactions related to low-density lipoproteins (LDL) apheresis**

In rare occasions, patients treated with ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulfate have shown life threatening anaphylactic reactions. These symptoms could be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.

**Hepatic impairment**

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. 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 lisinopril/hydrochlorothiazide who develop jaundice or marked elevations of hepatic

enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

**Surgery/anaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril 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.

**Metabolic and endocrine effects**

ACE inhibitor and thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

**Electrolyte imbalance**

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

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

**Hyperkalaemia**

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, 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 co-trimoxazole). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended**.**

**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**.**

**Hypersensitivity/angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with ACE inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with anti-histamines 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 patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE 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.

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

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

**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 reappeared upon inadvertent rechallenge.

**Neutropenia/agranulocytosis**

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for 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. Lisinopril 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 lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

**Race**

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

As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in non-black patients, 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.

**Lithium**

The combination of ACE inhibitors and lithium is generally not recommended. Anti-doping test

The hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

**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 anti-hypertensive 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.

**4.5 Drugs interactions Antihypertensive agents**

When combined with other antihypertensive agents, additive falls in blood pressure may occur. Concomitant use of glyceryl trinitrate and other nitrates or other vasodilators may further reduce the blood pressure.

The combination of lisinopril with aliskiren-containing medicines should be avoided.

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.

**Drugs that may increase 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.

**Lithium**

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

**Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels** The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels, particularly in patients with impaired renal function or diabetes mellitus, may lead to a significant increase in serum potassium. If concomitant use of lisinopril/hydrochlorothiazide and any of these agents is required, they should be used with caution and with frequent monitoring of serum potassium.

**Torsades de pointes-inducing medicinal products**

Because of the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicinal products that induce torsades de pointes, e.g. some antiarrhythmics, some anti-psychotics and other drugs known to induce torsades de pointes, should be used with caution.

**Tricyclic antidepressants/ antipsychotics /anaesthetics**

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure.

**Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid** Chronic administration of NSAID (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid >3 g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. NSAID and ACE inhibitors may exert an additive effect on the

increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

**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.

**Sympathomimetics**

Sympathomimetics can reduce the antihypertensive effect of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude

effectiveness of the pressor agent for therapeutic use.

**Antidiabetics**

Treatment with a thiazide diuretic may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal impairment. Other antidiabetic drugs including insulin requirements in diabetic patients may be increased, decreased, or unchanged.

The hyperglycaemic effect of diazoxide may be enhanced by thiazides.

**Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives**

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

**Calcium salts**

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and the dose adjusted accordingly.

**Cardiac glycosides**

Hypokalemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

**Colestyramine and colestipol**

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine. Therefore sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

**Non-depolarising muscle relaxants**

Thiazides may increase the responsiveness to non-depolarising skeletal muscle relaxants (e.g. tubocurarine).

**Trimethoprim**

Concomitant administration of ACE inhibitors and thiazides with trimethoprim increases

**Sotalol**

Thiazide induced hypokalaemia can increase the risk of sotalol induced arrhythmia.

**Allopurinol**

Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal damage and can lead to an increased risk of leucopoenia.

**Ciclosporin**

Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal damage and hyperkalaemia. Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications**.**

**Lovastatin**

Concomitant administration of ACE inhibitors and lovastatin increases the risk of hyperkalaemia.

**Cytostatics, immunosuppressives, procainamide**

Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

**Co-trimoxazole (trimethoprim/sulfamethoxazole)**

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia.

Thiazides may increase the risk of adverse effects caused by amantadine.

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.

**Ability to drive and use machines**

Lisinopril/hydrochlorothiazide combination products may have a mild to moderate effect on the ability to drive and use machines

**4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

**Pregnancy**

**ACE-inhibitors:**

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| The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy. |

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 inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti- hypertensive 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.

ACE inhibitor therapy exposure 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). Should

exposure to ACE inhibitors 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.

**Hydrochlorothiazide:**

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for primary hypertension in pregnant women except in rare situations where no other treatment could be used.

**Breast-feeding ACE-**

**inhibitors:**

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

**Hydrochlorothiazide:**

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of lisinopril/hydrochlorothiazide during breast feeding is not recommended. If lisinopril/hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

## 4.7 Effects on ability to drive and use machines

As with other antihypertensives, lisinopril/hydrochlorothiazide combination products may have a mild to moderate influence on the ability to drive and use machines. Especially at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these affects depend on the individual's susceptibility.

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 lisinopril and/or hydrochlorothiazide with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

The most commonly reported ADRs are cough, dizziness, hypotension, and headache which may occur in 1 to 10% of treated patients. In clinical studies, side effects have

usually been mild and transient, and in most instances have not required interruption of therapy.

**Lisinopril:**

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| **Blood and lymphatic system disorders:** | |
| Rare | Decreases in haemoglobin, decreases in haematocrit. |
| Very rare | Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, 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. |
| **Psychiatric disorders and nervous system disorders** | |
| Common | Dizziness, headache, syncope. |
| Uncommon | Paraesthesia, vertigo, taste disturbance, sleep disturbances, mood alterations, depressive symptoms. |
| Rare | Mental confusion, Olfactory disturbance. |
| Not known | Hallucinations. |
| **Cardiac and vascular disorders** | |
| Common | Orthostatic effects (including orthostatic hypotension). |
| Uncommon | Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, palpitations, tachycardia, Raynaud's syndrome. |
| Not known | Flushing. |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common | Cough |
| Uncommon | Rhinitis. |
| Very rare | Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia. |
| **Gastrointestinal disorders** | |
| Common | Diarrhoea, vomiting. |

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| Uncommon | Nausea, abdominal pain and indigestion. |
| Rare | Dry mouth. |
| Very rare | Pancreatitis, intestinal angioedema. |
| **Hepatobiliary disorders** | |
| Uncommon | Elevated liver enzymes and bilirubin. |
| Very rare | Hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure* |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon | Rash, pruritus. |
| Rare | Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, urticaria, alopecia, psoriasis. |
| Very rare | Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens- Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.** |
| **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 | Asthenia, fatigue. |
| **Investigations** | |
| Uncommon | Increases in blood urea, increases in serum creatinine, hyperkalaemia. |
| Rare | Hyponatraemia. |

* Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril/hydrochlorothiazide combination who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide combination and receive appropriate medical follow up.

** 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.

**Hydrochlorothiazide** (frequencies not known):

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| **Infections and infestations** | Sialadenitis. |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma). |
| **Blood and lymphatic system disorders** | Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression. |
| **Metabolism and nutrition disorders** | Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout. |
| **Psychiatric disorders** | Restlessness, depression, sleep disturbance. |
| **Nervous system disorders** | Loss of appetite, paraesthesia, light-headedness. |
| **Eye disorders** | Xanthopsia, transient blurred vision, acute myopia and acute angle-closure glaucoma. |
| **Ear and labyrinth disorders** | Vertigo. |
| **Cardiac disorders** | Postural hypotension. |
| **Vascular disorders** | Necrotising angiitis (vasculitis, cutaneous vasculitis). |
| **Respiratory, thoracic and mediastinal disorders** | Respiratory distress (including pneumonitis and pulmonary oedema). |
| **Gastrointestinal disorders** | Gastric irritation, diarrhoea, constipation, pancreatitis. |
| **Hepatobiliary disorders** | Jaundice (intrahepatic cholestatic jaundice). |
| **Skin and subcutaneous tissue disorders** | Photosensitivity reactions, rash, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis. |
| **usculoskeletal, connective tissue and bone disorders** | Muscle spasm, muscle weakness. |
| **Renal and urinary disorders** | Renal dysfunction, interstitial nephritits. |

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| **General disorders** | Fever, weakness. |

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

**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. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

## 4.9 Overdose

**Symptoms**

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.

Additional symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure.

If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

**Management**

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the supine 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 lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Bradycardia or extensive vagal reactions should be treated by administering atropine.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Mechanism of Action Lisinopril

Lisinopril 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.

**Hydrochlorothiazide**

Hydrochlorothiazide is a diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown.

## 5.2 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitor and diuretic ATC

code: C09BA03

Listril Plus is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

**Lisinopril**

Pharmacodynamic effects

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril 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 lisinopril remains to be elucidated.

Clinical efficacy and safety

*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.

**Hydrochlorothiazide**

Pharmacodynamic effects

Thiazides do not usually affect normal blood pressure.

Non-melanoma skin cancer

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

## 5.3 Pharmacokinetic properties

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

**Lisinpril**

**Absorption**

Following oral administration of lisinopril, 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 lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg) the absolute bioavailability is reduced approximately 16% in patients with heart failure.

Lisinopril absorption is not affected by the presence of food.

**Distribution**

Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzyme (ACE).

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

**Elimination**

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine.

On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril 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 lisinopril 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 lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min.

| Table 1 Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose | | | | | |
|---|---|---|---|---|---|
| **Renal Function Measured by creatinine clearance** | **n** | **Cmax (ng/ml)** | **Tmax (hr)** | **AUC (0-24 hrs) (ng/hr/ml)** | **$t_{1/2}$ (hr)** |
| >80 ml/min | 6 | 40.3 | 6 | 492+/-172 | 6.0+/-1.1 |
| 30-80 ml/min | 6 | 36.6 | 8 | 555+/-364 | 11.8+/-1.9 |
| 5-30 ml/min | 6 | 106.7 | 8 | 2228+/-938 | 19.5+/-5.2 |

With a creatinine clearance of 30-80ml/min, mean AUC was increased by 13% only, while a 4-5 fold increase in mean AUC was observed with creatinine clearance of 5- 30ml/min.

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril 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 lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

**Elderly**

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

**Hydrochlorothiazide**

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

## 6. NONCLINICAL PROPERTIES

### 6.1 Animal Toxicology or Pharmacology

Lisinopril and hydrochlorothiazide are both drugs on which extensive clinical experience has been obtained, both separately and in combination. All relevant information for the prescriber is provided elsewhere in the Prescribing Information.

## 7. DESCRIPTION

White to off white, round, biconvex, uncoated tablets, embossed with heart shaped on one side of the tablet and bisecting line on other side.

## 8. PHARMACEUTICAL PARTICULARS

### 8.1 Incompatibilities

Not applicable.

### 8.2 Shelf-life

2 Years. Do not use later than date of expiry

**8.3 Packaging information**

Available in strip pack of 10 tablets.

**8.4 Storage and handing instructions**

Store at a temperature not exceeding 25°C, protected from light and moisture. Keep all medicines out of reach of children.

**9. PATIENT COUNSELLING INFORMATION**

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet:**

a. What Listril Plus is and what it is used for
b. What you need to know before you take Listril Plus
c. How to take Listril Plus
d. Possible side effects
e. How to store Listril Plus
f. Contents of the pack and other information

**9.1 What Listril Plus is and what it is used for**

Listril Plus is used to treat high blood pressure (hypertension). It contains two medicines called lisinopril and hydrochlorothiazide.

Lisinopril belongs to a group of medicines called ACE inhibitors. It works by making your blood vessels widen.

Hydrochlorothiazide belongs to a group of medicines called diuretics (water tablets). It helps your body to get rid of water and salts like sodium in your urine.

These medicines work together to lower your blood pressure.

**9.2 What you need to know before you take Listril Plus Do not take Listril Plus:**

- if you are allergic to lisinopril or hydrochlorothiazide or any of the other ingredients of Listril Plus.
- if you are allergic to ACE inhibitor or sulphonamide medicines. If you are not sure if this applies to you, please ask your doctor.
- if you have ever had sudden swelling of the hands, feet, ankles, face, lips, tongue or throat, especially if this followed treatment with an ACE inhibitor. It may also have been difficult to swallow or breathe.
- if you have hereditary angioedema (a condition that makes you more prone to the swelling described above). If you are not sure if this applies to you, please ask your doctor.

• if you have severe kidney problems.

• if you have stopped passing water (urine).

• if you have severe liver problems.

• if you are more than 3 months pregnant. (It is also better to avoid Listril Plus in early pregnancy - see the sections on 'Pregnancy and breast-feeding').

• if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Do not take Listril Plus if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Listril Plus.

**Warnings and precautions**

Talk to your doctor or pharmacist before taking Listril Plus:

• if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Listril Plus.

• if you have a narrowing (stenosis) of the aorta (an artery in your heart), the heart valves (mitral valves) or the kidney artery.

• if you have an increase in the thickness of the heart muscle (known as hypertrophic cardiomyopathy).

• if you have problems with your blood vessels (collagen vascular disease).

• if you have low blood pressure. You may notice this as feeling dizzy or light-headed, especially when standing up.

• if you have kidney problems or you are having kidney dialysis or you have had a kidney transplant.

• if you have liver problems.

• if you have diabetes.

• if you are taking any of the following medicines used to treat high blood pressure:

o an angiotensin II receptor blocker (ARBs) (also known as sartans – for example valsartan, telmisartan, irbesartan), in particular if you have diabetesrelated kidney problems.

o aliskiren.

Your doctor may check your kidney function, blood pressure and the amount of electrolytes (e.g. potassium) in your blood at regular intervals. See also information under the heading "Do not take Listril Plus".

• if you have recently had diarrhoea or vomiting (being sick).

• if your doctor has told you to control the amount of salt in your diet.

• if you have high levels of cholesterol and you are having a treatment called 'LDL apheresis'.

• if you have ever had a condition called systemic lupus erythematosus (SLE).

• if you are of black origin as Listril Plus may be less effective. You may also more readily get the side effect 'angioedema' (a severe allergic reaction with swelling of the hands, feet, ankles, face, lips, tongue or throat).

• if you are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in area such as the throat) is increased:

- sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs).

You must tell your doctor if you think you are (or might become) pregnant. Listril Plus is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see the sections on 'Pregnancy and breast-feeding').

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Listril Plus

**Treatment for allergies such as insect stings**

Tell your doctor if you are having or are going to have treatment to lower the effects of an allergy such as insect stings (desensitisation treatment). If you take Listril Plus while you are having this treatment, it may cause a severe allergic reaction.

**Operations**

If you are going to have an operation (including dental surgery) tell the doctor or dentist that you are taking Listril Plus. This is because you can get low blood pressure (hypotension) if you are given certain local or general anaesthetics while you are taking Listril Plus.

Other medicines and Listril Plus

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Listril Plus can affect the way some medicines work and some medicines can have an effect on Listril Plus. Your doctor may need to change your dose and/or to take other precautions.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

• Other medicines for treatment of high blood pressure (antihypertensives).

• An angiotensin II receptor blocker (ARB) or aliskiren, (see also information under the headings "Do not take Listril Plus" and "Warnings and precautions").

• Medicines associated with low blood potassium (hypokalaemia) such as other diuretics ("water tablets" including those which conserve potassium, laxatives, corticosteroids (e.g. prednisone), ACTH (A hormone), amphotericin (an antifungal medicine) and salicylic acid derivatives.

• Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen or indomethacin, used to treat muscle pain or arthritis.

• Medicines for depression (tricyclic and tetracyclic antidepressants).

• Medicines for mental problems such as lithium.

• Aspirin (acetylsalicylic acid), if you are taking more than 3 grams each day.

• Potassium supplements, salt substitutes containing potassium or other medicines which can increase the amount of potassium in your body.

• Heparin (a medicine for thinning the blood).

• Co-trimoxazole (an antibiotic medicine) also known as trimethoprim/sulfamethoxazole.

• Calcium salts or Vitamin D supplements.

- Medicines for diabetes (insulin and oral antidiabetics such as sulphonylureas). Your dose of antidiabetic medicine may need to be changed when taking thiazide diuretics.
- Medicines to treat asthma.
- Medicines to treat nose or sinus congestion or other cold remedies (including those you can buy in the pharmacy).
- Medicines to suppress the body's immune response (immunosuppressants, such as ciclosporin).
- Allopurinol (for gout).
- Medicines for uneven heart beat problems (such as procainamide).
- Heart medicines (e.g. digoxin) or other medicines to control the rhythm of your heart.
- Gold injections (such as sodium aurothiomalate), usually used to treat rheumatoid arthritis.
- Amphotericin B injection (to treat fungal infections).
- Carbenoxolone (to treat ulcers or inflammation in the gullet or in and around the mouth).
- Corticosteroids (steroid medicines).
- Corticotropin (a hormone).
- Medicines to treat constipation (stimulant laxatives).
- Colestyramine and colestipol (to lower cholesterol, prevent diarrhoea or reduce itching).
- Muscle relaxants such as tubocurarine.
- Trimethoprim (an antibiotic).
- Sotalol (a beta-blocker).
- Lovastatin (to lower cholesterol).
- Dextran sulphate (used in the treatment called 'LDL apheresis' to lower cholesterol).

The following medicines may increase the risk of angioedema (signs of angioedema include swelling of the face, lips, tongue and/or throat with difficulty in swallowing or breathing):

- Medicines to break up blood clots (tissue plasminogen activator), usually given in hospital.
- Medicines which are most often used to avoid rejection of transplanted organs (sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors).
- Racecadotril used to treat diarrhoea.
- Other medicines known to have an effect on the heart called Torsades de pointes.

Low blood pressure may be aggravated by alcohol, barbiturates or anaesthetics. You may notice dizziness when standing up.

**Pregnancy and breast-feeding**

*Pregnancy*

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Listril Plus before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Listril

Plus. Listril Plus is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of

pregnancy.

*Breast-feeding*

Tell your doctor if you are breast-feeding or about to start breast-feeding. Listril Plus is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely

**Driving and using machines**

• This medicine may cause occasional dizziness or tiredness which may have an effect on your ability to drive or use machines, especially at the start of treatment or when the dose is adjusted, or in combination with alcohol. If this happens to you, do not drive or use any tools or machines.

• You must wait to see how your medicine affects you before trying these activities.

## 9.3 How to take Listril Plus

Always take Listril Plus exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Once you have started taking Listril Plus your doctor may take blood tests. Your doctor may then adjust your dose so you take the right amount of medicine for you.

**Taking your medicine**

• Swallow the tablet with a drink of water.

• Try to take your tablets at the same time each day. It does not matter if you take Listril Plus before or after food.

• Keep taking Listril Plus for as long as your doctor tells you to, it is a long term treatment. It is important to keep taking Listril Plus every day.

**Taking your first dose**

• Take special care when you have your first dose of Listril Plus or if your dose is increased. It may cause a greater fall in blood pressure than later doses.

• This may make you feel dizzy or light-headed. If this happens, it may help to lie down. If you are concerned, please talk to your doctor as soon as possible.

**Adults**

• The recommended dose is one tablet once a day. Your doctor will prescribe the tablet that is the right strength for you.

• If necessary, your doctor may increase your dose to two tablets once a day.

**Use in children**

• Listril Plus is not recommended for use in children.

**If you take more Listril Plus than you should**

If you take more Listril Plus than prescribed by your doctor, talk to a doctor or go to a hospital immediately. Take the medicine pack with you so that the tablets can be identified.

**If you forget to take Listril Plus**

• If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose.

• Do not take a double dose to make up for a forgotten dose.

**If you stop taking Listril Plus**

Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Listril Plus contains two medicines: lisinopril and hydrochlorothiazide. The following side effects have been seen with these individual medicines. This means they could also happen with Listril Plus.

Your doctor may take blood samples from time to time to check whether Listril Plus has had any effect on your blood.

**Possible side effects with lisinopril**

**Severe allergic reactions** (rare, may affect up to 1 in 1,000 people)

If you have a severe allergic reaction, **stop taking Listril Plus and see a doctor immediately.**

The signs may include sudden onset of:

• Swelling of your face, lips, tongue or throat. This may make it difficult to swallow.

• Severe or sudden swelling of your hands, feet or ankles.

• Difficulty breathing.

• Severe itching of the skin (with raised lumps).

**Severe liver problems** (very rare, may affect up to 1 in 10,000 people) The signs may include:

• Yellowing of your skin or eyes, dark coloured urine or a loss of appetite. If this happens to you, **see a doctor immediately.**

**Other possible side effects:**

**Common (may affect up to 1 in 10 people)**

• Headache.

• Feeling dizzy or light-headed, especially if you stand up quickly.

• Fainting.

• Diarrhoea.

• Being sick (vomiting).

• Cough.

• Kidney problems (shown in a blood test).

**Uncommon (may affect up to 1 in 100 people)**

• Mood changes including feeling depressed.

• Tingling feeling such as ‘pins and needles’.

• Spinning feeling (vertigo).

• Changes in the way things taste.

• Difficulty in sleeping.

• A very big drop in blood pressure may happen in people with the following conditions: coronary heart disease; narrowing of the aorta (a heart artery), kidney artery or heart valves; an increase in the thickness of the heart muscle. If this happens to you, you may feel dizzy or light-headed, especially if you stand up quickly.

• Heart attack or stroke.

• Unusual heart beat.

• Change of colour in your fingers or toes.

• Runny nose.

• Feeling sick (nausea).

• Stomach pain and indigestion.

• Changes in blood tests that check how the liver is working.

• Rash.

• Itching

• Being unable to get an erection (impotence).

• Feeling weak.

• Feeling tired.

• Increased levels of certain substances in your blood (urea, creatinine or potassium).

**Rare (may affect up to 1 in 1,000 people)**

• Changes to some of the cells or other parts of your blood. The signs may include feeling tired and pale skin.

• Feeling confused.

• Changes in the way things smell.

• Dry mouth.

• Skin rash with dark red, raised, itchy bumps (hives).

• Hair loss (alopecia).

• Psoriasis (a skin problem).

• Infection of the blood.

• Kidney failure.

• Enlarged breasts in men.

• Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

• Low levels of sodium in the blood, which may cause weakness, tiredness, headache, feeling sick, being sick (vomiting) and cramps.

**Very rare (may affect up to 1 in 10,000 people)**

• Problems with your bone marrow or a reduced number of blood cells and/or platelets in your blood. You may notice tiredness, an infection (which may be serious), fever, feeling breathless or that you bruise or bleed more easily.

• Swollen glands (lymph nodes).

• Increased immune response (autoimmune disease).

• Low levels of sugar in your blood (hypoglycaemia). The signs may include feeling hungry or weak, sweating and a fast heartbeat.

• Suddenly feeling wheezy or short of breath (bronchospasm).

• Lung inflammation (which may make you feel breathless).

• Sinusitis (a feeling of pain and fullness behind your cheeks and eyes).

• Eosinophilic pneumonia. The signs include a combination of the following:

- sinusitis
- feeling like you have flu
- feeling more and more breathless
- pain in the area of your stomach or gut
- skin rash
- a feeling of 'pins and needles' or numbness of your arms or legs.

• Inflammation of the pancreas. This causes moderate to severe pain in the stomach.

• Swelling of the lining of the gut. This may cause sudden stomach pain, diarrhoea or make you be sick (vomit).

• Sweating.

• Severe skin disorder or rash. The symptoms include redness, blistering and peeling of the skin which may develop quickly and may include blistering in the mouth and nose.

• Passing less water (urine) than normal or passing no water.

**Not known (frequency cannot be estimated from the available data)**

• Seeing, feeling or hearing things that are not there (hallucinations).

• Flushing of your skin.

**Possible side effects with hydrochlorothiazide (frequency not known)**

• Skin and lip cancer (Non-melanoma skin cancer).

• Inflammation of a salivary gland.

• A reduced number of blood cells and/or platelets in your blood. You may notice tiredness, an infection (which may be serious), fever, feeling breathless or that you bruise or bleed more easily.

• Loss of appetite.

• An increase in the amount of sugar (glucose) in your blood (hyperglycaemia).

• Sugar in your urine.

• An increase in the amount of uric acid in your blood.

• Altered levels of substances in your blood (for example low sodium and potassium). You may notice muscle weakness, thirst, 'pins and needles', cramps or feeling sick.

• Raised or high levels of fats in your blood (including cholesterol).

• Feeling restless.

• Depression.

• Difficulty sleeping.

• Tingling feelings such as 'pins and needles'.

• Feeling light headed.

• Changes to your vision that can make things look yellow.

• Problems with your sight for a short time.

• Severe eye pain with redness and sudden blurred vision. If you have a suddenly painful red eye tell your doctor immediately; you may need treatment to avoid permanent loss of vision

• A spinning feeling (vertigo).

• Feeling faint (especially when standing up).

• Damage to blood vessels causing red or purple spots in the skin.

• Difficulty breathing. You may feel breathless if your lungs get inflamed or have fluid on them.

• Stomach irritation.

• Diarrhoea.

• Constipation.

• Inflammation of the pancreas. This causes moderate to severe pain in the stomach.

• Yellowing of your skin or the whites of your eyes (jaundice).

• Skin problems including rash caused by sensitivity to sunlight, rash, severe rash that develops quickly with blistering or peeling of the skin and possibly blistering in the mouth, activating or worsening of existing lupus conditions or appearance of unusual skin reactions.

• Allergic reactions.

• Muscle cramps and muscle weakness.

• Kidney problems which may be severe (shown in blood tests).

• Fever.

• Weakness.

Do not be concerned by this list of possible side effects. You may not get any of them.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

## 9.5 How to store Listril Plus

• Keep this medicine out of the sight and reach of children.

• Do not use this medicine after the expiry date which is stated on the blister strip and the carton. The expiry date refers to the last day of that month.

• Store at a temperature not exceeding 25°C, protected from light and moisture.

• Do not throw away any medicines via wastewater or household waste. Ask your pharmacist

how to throw away medicines you no longer use. These measures will help protect the environment.

**9.6 Contents of the pack and other information**

**What Listril Plus contains**

The active substances are Lisinopril and Hydrochlorothiazide Tablets

Listril Plus Tablets contains 5 mg of lisinopril and 12.5 mg of hydrochlorothiazide

The other ingredients are Disodium Hydrogen Ortho Phosphate, Magnesium Stearate, Talc, Pregelatinized Starch, Mannitol and Starch.

**What Listril Plus looks like and contents of the pack**

Listril Plus Tablets are white to off white, round, biconvex, uncoated tablets, embossed with heart shaped on one side of the tablet and bisecting line on other side.

They are available in strip pack of 10 tablets.

**10. DETAILS OF MANUFACTURER**

TORRENT PHARMACEUTICALS LTD.

32 No, Middle Camp, NH-10,

East District, Gangtok , Sikkim-737 135.

Or

Innova Captab Limited

Kh No. 1281/1, Hilltop,

Industrial Estate, Nr. EPIP, Phase-1,

Jharmajri, Baddi, Distt. Solan

(H.P.)-173205.

**11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

Mfg Lic No.: M/563/2010 issued on 06.12.2021

Or

Mfg Lic No.: MNB/16/970 issued on 18.12.2020

**12. DATE OF REVISION**

Aug 2022

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

**IN/LISTRIL PLUS 5, 12.5 mg/AUG-2022/07/PI**