IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0818/001/001
Case No: 2028204

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Medimpex (UK) Limited

127 Shirland Road, **London W9 2EP**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

TENSOPRIL Tablets 12.5mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/10/2006** until **18/02/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tensopril Tablets 12.5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.5mg captopril.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White or greyish white, flat, disc-shaped, bevelled edge tablet with a score line on one side and ‘E121’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: Captopril is indicated for the first line treatment of mild to moderate hypertension.

In severe hypertension captopril should be used where standard therapy is ineffective or inappropriate.

Congestive heart failure: In the treatment of congestive heart failure, captopril should be used in combination with diuretics, and where appropriate, digitalis.

4.2 Posology and method of administration

The anti-hypertensive effect of captopril is not affected by food.

Hypertension: The lowest effective dosage should be used, by titration to the requirements of each patient.

Mild to moderate hypertension: Treatment should be started at 12.5mg twice daily or 25mg once daily. The usual maintenance dose is 25mg twice daily, which can be titrated upwards, at 2-4 week intervals, to achieve optimal blood pressure control. The maximum recommended dosage is 50mg twice daily.

Severe hypertension: Treatment should be started at 12.5mg twice daily or 25mg once daily in patients where standard therapy has been ineffective or has resulted in unacceptable adverse effects.

Captopril should be used in combination with other antihypertensive agents and the dose of these should be adjusted for each patient. The dosage of captopril may be increased incrementally to a maximum of 50mg tid. A total daily dose of 150mg captopril should not normally be exceeded.

Congestive heart failure: Captopril therapy must be initiated under close medical supervision. Captopril should be introduced when diuretic therapy does not adequately control symptoms. Treatment should begin with a dose of 6.25mg (half a 12.5mg tablet) or 12.5mg, in order to minimise the risk of a hypotensive episode. As an additional precaution, diuretic treatment should be discontinued or reduced before captopril treatment is started, if possible.

The usual maintenance dose is 25mg two or three times daily. This can be increased incrementally until a satisfactory

response is achieved. An interval of at least two weeks should be allowed between each dose increase. The usual maximum daily dose is 150mg.

Elderly: No specific dosage adjustment is required in the elderly, unless the patient has concomitant renal impairment. Renal function must be assessed (see 4.4 'Special warnings and special precautions for use') prior to starting treatment. The dose should be titrated to the lowest possible dose which achieves adequate blood pressure control.

Children: Captopril is not recommended for the treatment of mild to moderate hypertension in children.

There is limited experience of captopril in neonates. Renal function in neonates and infants is not equivalent to that of older children and adults, so lower doses should be used and the patient should be under close medical supervision.

When clinically indicated, the starting dose should be 0.3mg/kg bodyweight up to a maximum of 6mg/kg bodyweight daily, in divided doses. The dose should be adjusted depending on the response of each patient and can be given two or three times daily.

Patients with renal impairment: Captopril elimination correlates with creatinine clearance. Therefore, when clinically indicated in severely hypertensive patients with impaired renal function, dose should be adjusted according to renal function, by reducing the total daily dose or increasing the dosage interval. In patients with severe renal impairment (creatinine clearance less than 30ml/min/1.73m^2), the initial daily dose should be 12.5mg bd. The dose should be titrated to the lowest possible dose which achieves adequate blood pressure control.

Captopril is dialysable.

4.3 Contraindications

Hypersensitivity to the product or any other ACE inhibitor. History of angioneurotic oedema associated with previous ACE inhibitor therapy. Aortic stenosis or outflow obstruction.

Captopril is contra-indicated in pregnancy and in nursing mothers. It should not be used in women of child bearing potential unless effective contraceptive methods are used. (See 4.6 'Pregnancy and lactation' for further information).

Exposure of the mother in the second and third trimesters of pregnancy has been associated with oligohydramnios and neonatal hypotension and/or anuria.

4.4 Special warnings and precautions for use

Assessment of renal function: The incidence of adverse reactions associated with captopril administration is principally related to renal function, since the drug is excreted primarily by the kidney. Therefore, before starting treatment with captopril, evaluation of the patient should include assessment of renal function. This assessment should also be performed at appropriate intervals during treatment.

Impaired renal function: When clinically indicated in severely hypertensive patients, the dose should be adjusted (See 4.2 'Posology and method of administration') and close monitoring of renal function during therapy should be performed as deemed appropriate.

Renal: Proteinuria is rare in patients with prior normal renal function. Where proteinuria has occurred, it has usually been in patients with severe hypertension and evidence of prior renal disease. Nephrotic syndrome occurred in some of these patients.

Although membranous glomerulopathy was found in biopsies taken from some proteinuric patients, a casual relationship to captopril has not been established.

Increased concentrations of blood urea and serum creatinine have been reported in some patients with renal disease (particularly those with bilateral renal artery stenosis or unilateral renal artery stenosis in a single functioning kidney). For some of these patients it may not be possible to normalise blood pressure and maintain adequate renal perfusion.

These increases in concentrations of blood urea and serum creatinine have also been reported in some patients with no apparent pre-existing renal disease, when a diuretic has been given concomitantly with an ACE inhibitor. This situation should alert the clinician to the possibility of underlying renal artery stenosis. Captopril dosage reduction and/or discontinuation of the diuretic may be required.

Patients who are dialysed using high-flux polyacrylonitrile membranes and are treated with ACE inhibitors have experienced a high incidence of anaphylactoid reactions e.g. facial swelling, flushing, hypotension, and dyspnoea, within a few minutes of commencing dialysis. It is recommended to use an alternative membrane or an alternative anti-hypertensive drug.

Symptomatic hypotension: Patients may experience symptomatic hypotension, especially after the first one or two doses of captopril. This is rare in uncomplicated hypertension. Hypotensive responses usually occur within one hour of the initial dose of captopril and have been reported mainly in patients with severe and renin dependent hypertension or heart failure, with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatraemia or functional renal impairment.

The possibility of symptomatic hypotension may be reduced by discontinuing or reducing the diuretic therapy for four to seven days before initiating captopril therapy with small doses.

Similar precautions and close supervision may also apply to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident. Symptomatic hypotension may also occur in patients who have been volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting.

If hypotension develops, the patient should be placed in the supine position. Volume repletion with intravenous normal saline may be required.

The appearance of first dose hypotension does not preclude subsequent careful dose titration with captopril.

Angioedema: of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors. In such cases, captopril should be discontinued and the patient observed. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous adrenaline (0.5ml, 1:1,000) should be administered promptly where indicated.

Cough: During treatment with an ACE inhibitor, a dry non-productive cough may occur which disappears after discontinuation of treatment.

Hyperkalaemia: This may occur during treatment with an ACE inhibitor, especially in the presence of renal insufficiency and/or heart failure.

Potassium supplements or potassium sparing diuretics are not recommended, since they may lead to significant increase in serum potassium.

Surgery/anaesthesia: In patients undergoing surgery, or during anaesthesia with agents which produce hypotension, captopril will block angiotensin II formation secondary to compensatory rennin release. This may lead to hypotension which can be corrected by volume expansion.

General: Captopril should not be used in patients with aortic stenosis or outflow obstruction.

As there is limited information in the treatment of acute hypertensive crises, the use of captopril should be avoided in these patients.

Neutropenia/agranulocytosis: Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving captopril treatment. Neutropenia is rarely seen in patients with normal renal function and no other

complicating factors.

Captopril should not be used in patients with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma, in patients receiving immunosuppressive therapy, in patients treated with allopurinol or procainamide, or a combination of these factors. Some such patients developed serious infections which, in a few cases, did not respond to intensive antibiotic therapy. In most patients neutrophil counts rapidly returned to normal upon discontinuing captopril.

When captopril is clinically indicated in the above patient categories, white blood cell count and differential counts should be performed prior to therapy, every two weeks for the first 3 months of treatment then at regular suitable intervals. All patients should be instructed to report any sign of infection, when a differential white blood cell count should be performed. If neutropenia is detected or suspected captopril should be withdrawn.

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

4.5 Interaction with other medicinal products and other forms of interaction

Associations not recommended: Use with potassium-sparing diuretics or potassium supplements is not recommended. Significant increase in serum potassium may result from concurrent use of potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes. If hypokalaemia necessitates their use, they should be used with caution and serum potassium monitored frequently.

Concomitant administration of ACE-inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increase in blood glucose lowering effect with the risk of hypoglycaemia.

This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Precautions for use:

Diuretics: After captopril treatment has started, excessive reduction in blood pressure may occur in patients receiving diuretics and particularly those who are volume-and/or salt-depleted. Risk of hypotensive effects may be reduced by:

- stopping diuretic treatment;
- increasing volume or salt intake before administration of the ACE inhibitor;
- starting treatment with lower doses of captopril and increasing dosage, if necessary with caution.

Lithium: Excretion of lithium may be reduced if lithium and captopril are administered concomitantly. Frequent monitoring of serum lithium levels should be performed.

Narcotic drugs/antipsychotics: Postural hypotension may result.

Antihypertensive agents: The hypotensive effect of ACE inhibitors is increased.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids, or procainamide: The risk of leucopenia may be increased if used concomitantly with ACE inhibitors.

Associations (interactions) to be taken into account:

Non-steroidal anti-inflammatory drugs (NSAIDs): The antihypertensive effect of an ACE inhibitor may be reduced by administration of an NSAID. An additive effect on serum potassium increase has been described when NSAIDs and ACE inhibitors are used concomitantly, while renal function may be reduced. Such effects, which occur particularly in patients with compromised renal function are, in principle, reversible.

Antidiabetic agents: ACE-inhibitors have been shown to enhance insulin sensitivity. There have been rare reports of hypoglycaemic episodes in diabetic patients treated concomitantly with ACE-inhibitors and antidiabetic medicines (insulin, oral hypoglycaemic agents). In such cases, a reduction in the dose of the antidiabetic medicine may be required.

Antacids: Cause reduced bioavailability of ACE inhibitors.

Sympathomimetics: The antihypertensive effects of ACE inhibitors may be reduced. To confirm the required effect is obtained, patients should be carefully monitored.

Probenecid: Delays renal excretion and therefore may increase blood levels of captopril.

Alcohol: The hypotensive effect of ACE inhibitors is increased.

Food: The bioavailability of captopril may be decreased.

4.6 Pregnancy and lactation

No appropriate and well-controlled clinical studies have been performed in humans. Therefore captopril should not be used during pregnancy.

Animal studies suggest that captopril has the potential to cause foetotoxicity. Foetal and neonatal morbidity and mortality may occur when ACE inhibitors (these can cross the placenta) are administered to pregnant women.

Neonatal hypotension, renal failure, face or skull deformities and/or death have been associated with exposure of the foetus during the second and third trimesters. Maternal oligohydramnios (indicative of decreasing foetal renal function) has been reported. Reports of limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation have been associated with oligohydramnios.

Close observation of infants exposed in utero for hypotension, oliguria, and hyperkalaemia should be carried out. If oliguria occurs, treatment should consist of support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus, and foetal death have been reported, but their relationship to ACE inhibition or the underlying maternal disease in unknown.

The effect of exposure of the foetus during the first trimester is unknown. If pregnancy occurs during treatment the woman should be informed of the possible hazard to the foetus.

Use of captopril during breast feeding by lactating mothers is not recommended (captopril may be excreted in breast milk and the effects on the nursing infant are unknown).

4.7 Effects on ability to drive and use machines

There are no studies on the effect of ACE inhibitors on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Cardiovascular: Symptomatic hypotension (See 4.4 'Special warnings and special precautions for use') including symptoms like dizziness, feeling of weakness, impaired vision, rarely with disturbance of consciousness can occur. Rhythm disturbances, palpitations, angina pectoris, myocardial infarction, transient ischaemic attacks and cerebral haemorrhage have been reported only rarely for ACE inhibitors, in association with hypotension.

Renal: Renal insufficiency may occur or be intensified. Acute renal failure has been reported (See 4.4 'Special warnings and special precautions for use' and '*Drug/laboratory parameters'* below).

Respiratory: Non-productive cough and rarely, bronchospasm, dyspnoea, sinusitis, rhinitis, glossitis and bronchitis have been reported. In individual cases angioneurotic oedema involving the upper airways has caused fatal airways obstruction.

Gastrointestinal: Taste disturbance, which is reversible and usually self-limiting, has been reported. Weight loss (possibly associated with loss of taste), stomatitis (resembling aphthous ulcers) and occasionally, nausea, vomiting, dyspepsia, diarrhoea or constipation can occur. Raised liver enzymes have been detected in a few patients. Hepatocellular injury and cholestatic jaundice have been rarely reported. Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has been fatal.

Skin: Occasionally, allergic and hypersensitivity reactions can occur e.g. rash which is usually pruritic, mild, transient and macropapular, rarely urticarial. Dosage reduction, treatment with an antihistamine and/or discontinuing therapy will resolve the rash within a few days.

In a few cases the reaction has been associated with fever, myalgia, arthralgia, eosinophilia and/or increased ANA titres. Pruritus, flushing, vesicular or bullous rash and photosensitivity have been reported.

Nervous system: Occasionally: headaches, dizziness, weariness and taste disturbances; rarely: depression, sleep disorders, impotence, disorders of balance, confusion, tinnitus and very rarely blurred vision occur.

Other: Paraesthesias of the hands, serum sickness and lymphadenopathy have been reported.

Drug/laboratory parameters: Increases in blood urea and plasma creatinine, reversible on discontinuation occur, especially in the presence or renal insufficiency, severe heart failure and renovascular hypertension. Proteinuria, elevated serum potassium and acidosis have occurred.

Decreases in haemoglobin, haematocrit, platelets, and white cell count, and in individual cases agranulocytosis or pancytopenia, as well as elevation of liver enzymes and serum bilirubin have been reported in a few patients.

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

After ingestion of an overdose, the patient should be kept under close supervision. Serum electrolyte and creatinine should be monitored frequently. Measures to prevent absorption and hasten elimination should be applied if ingestion is recent. If hypotension develops, the patient should be placed in the shock position then volume expansion is the treatment of choice. Captopril is removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Captopril is a highly specific competitive inhibitor of angiotensin I-converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal to secrete aldosterone). The beneficial effects of ACE inhibitors in hypertension and heart failure appear to result primarily from the suppression of the renin-angiotensin aldosterone system.

ACE inhibition results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system.

In patients with hypertension administration of ACE inhibitors results in a reduction of supine and standing blood pressure to about the same extent with no compensatory increase in heart rate. Peripheral arterial resistance is reduced with no clinically significant changes in cardiac output.

The haemodynamic effects of ACE inhibitors therapy in patients with heart failure result from both arteriolar and veno-dilatation. Thus, pre-and after-load are reduced. Consequences are a decrease in left ventricular filling pressure/capillary wedge pressure and an increase in cardiac output. Clinically, signs and symptoms of heart failure will improve and exercise capacity increase. These effects are maintained during long-term treatment.

5.2 Pharmacokinetic properties

In healthy fasting subjects 70% of an oral dose is absorbed and the absolute bioavailability is about 60% compared with the IV route. With a single oral dose there is a dose to plasma level (C_{max} and AUC) relationship over the range 10 to 100mg.

Following a single oral dose of 100mg C_{max} is about 1.6 to 1.9mg/ml. T_{max} is about 0.8 to 1.0 hour. In respect of ACE inhibitors the effective plasma half life is 2 hours. The onset of action from an oral dose is 30 minutes, with the maximal effect observed at 1-2 hours. Antihypertensive efficacy is not approved by doses in excess of 150 mg daily.

Co-administration with food decreases the bioavailability by 25-50% but has not impact on the antihypertensive effect.

5.3 Preclinical safety data

Acute/repeat dose toxicity: Since captopril has been available for clinical use since 1981, it is considered that the experience gained over the years in humans now outweighs the pre-clinical data. The relevant aspects are all described earlier in the SPC.

Reproduction studies: Captopril has been demonstrated to be lethal to rabbit and sheep foetuses. No foetotoxic effects were observed on hamster or rat foetuses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline cellulose
Maize starch
Hydrogenated castor oil
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

48 months.

6.4 Special precautions for storage

Do not store above 30°C.
Keep in the original package.

6.5 Nature and contents of container

Blister strip packs (PVC/PVdC/aluminium foil).
Each blister strip contains 10 or 14 tablets presented in cardboard cartons of 28, 30, 56, 60, 90 and 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Medimpex UK Ltd,
127 Shirland Road,
London, W9 2EP,
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8 MARKETING AUTHORISATION NUMBER

PA 818/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th February 1999
Date of last renewal: 19th February 2004

10 DATE OF REVISION OF THE TEXT

November 2004