IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA0465/219/001
Case No: 2063450

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Natrilix SR 1.5mg prolonged-release film-coated tablets

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 **14/08/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Natrilix SR 1.5mg prolonged-release film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indapamide 1.5 mg per prolonged-release film-coated tablet.

Excipients: 124.5 mg lactose monohydrate.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, film coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Essential hypertension.

4.2 Posology and method of administration

Oral use.

One tablet per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed.
At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

Renal failure (see sections 4.3 and 4.4):
In severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated.
Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired.

Elderly (see section 4.4):
In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with Natrilix SR when renal function is normal or only minimally impaired.

Patients with hepatic impairment (see sections 4.3 and 4.4):
In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:
Natrilix SR is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients.
- Severe renal failure.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.

4.4 Special warnings and precautions for use

Special warnings

When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy, particularly in case of electrolyte imbalance. Administration of the diuretic must be stopped immediately if this occurs.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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

Special precautions for use

- **Water and electrolyte balance:**

• Plasma sodium:

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (see sections 4.8 and 4.9).

• Plasma potassium:

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk populations, *i.e*. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal *torsades de pointes.*

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.
Detection of hypokalaemia requires its correction.

• Plasma calcium:

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.
Treatment should be withdrawn before the investigation of parathyroid function.

- **Blood glucose:**

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

- **Uric acid:**

Tendency to gout attacks may be increased in hyperuricaemic patients.

- **Renal function and diuretics:**

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, *i.e*. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.

Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen preexisting renal insufficiency.

- **Athletes:**

The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:

Increased plasma lithium with signs of overdosage, as with a salt-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment are required.

Combinations requiring precautions for use:

Torsades de pointes-inducing drugs:

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide),
- some antipsychotics :

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
benzamides (amisulpride, sulpiride, sultopride, tiapride)
butyrophenones (droperidol, haloperidol)
others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.

Increased risk of ventricular arrhythmias, particularly torsades de pointes (hypokalaemia is a risk factor).
Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.

Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

N.S.A.I.Ds. (systemic route) including COX-2 selective inhibitors, high dose salicylic acid (≥ 3 g/day):

Possible reduction in the antihypertensive effect of indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration). Hydrate the patient; monitor renal function at the start of treatment.

Angiotensin converting enzyme (A.C.E.) inhibitors:

Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. is initiated in the presence of preexisting sodium depletion (particularly in patients with renal artery stenosis).

In hypertension, when prior diuretic treatment may have caused sodium depletion, it is necessary:
- either to stop the diuretic 3 days before starting treatment with the A.C.E. inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the A.C.E. inhibitor and increase the dose gradually.

In congestive heart failure, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.

In all cases, monitor renal function (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives:

Increased risk of hypokalaemia (additive effect).
Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

Baclofen:

Increased antihypertensive effect.
Hydrate the patient; monitor renal function at the start of treatment.

Digitalis preparations:

Hypokalaemia predisposing to the toxic effects of digitalis.
Monitoring of plasma potassium and ECG and, if necessary, adjust the treatment.

Combinations to be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):

Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin:

Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/l) in women.

Iodinated contrast media:

In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration before administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics:

Antihypertensive effect and increased risk of orthostatic hypotension increased (additive effect).

Calcium (salts):

Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Ciclosporin, tacrolimus:

Risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route):

Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 Pregnancy and lactation

Pregnancy:

As a general rule, the administration of diuretics should be avoided in pregnant women and should never be used to treat physiological oedema of pregnancy. Diuretics can cause foetoplacental ischaemia, with a risk of impaired foetal growth.

Lactation:

Breast-feeding is inadvisable (Indapamide is excreted in human milk).

4.7 Effects on ability to drive and use machines

Indapamide does not affect vigilance but different reactions in relation with the decrease in blood pressure may occur in individual cases, especially at the start of the treatment or when another antihypertensive agent is added.
As a result the ability to drive vehicles or to operate machinery may be impaired.

4.8 Undesirable effects

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent.

Thiazide-related diuretics, including indapamide, may cause the following undesirable effects ranked under the following frequency:
Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:
Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Nervous system disorders:
Rare: vertigo, fatigue, headache, paresthesia

Cardiac disorders:
Very rare: arrhythmia, hypotension.

Gastrointestinal disorders:
Uncommon: vomiting
Rare: nausea, constipation, dry mouth
Very rare: pancreatitis

Renal and urinary disorders:
Very rare: renal failure

Hepato-biliary disorders:
Very rare: abnormal hepatic function
Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)

Skin and subcutaneous tissue disorders:
Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:
- Common: maculopapular rashes
- Uncommon: purpura
- Very rare: angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome
Not known: possible worsening of pre-existing acute disseminated lupus erythematosus.
Cases of photosensitivity reactions have been reported (see section 4.4).

Laboratory parameters :
During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/l) was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
Very rare : Hypercalcaemia
Not known:
- Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4).
- Hyponatraemia with hypovolaemia responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.
- Increase in plasma uric acid and blood glucose during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes.

4.9 Overdose

Indapamide has been found free of toxicity at up to 40 mg, *i.e*. 27 times the therapeutic dose.
Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).
Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain
ATC code: C 03 BA 11

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.

The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.
Indapamide reduces left ventricular hypertrophy.
Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.

It has also been shown, in the short-, mid- and long-term in hypertensive patients, that indapamide:
- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;
- does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

5.2 Pharmacokinetic properties

Indapamide 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within a support which allows sustained release of indapamide.

Absorption:
The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.

Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed.
Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

Distribution:
Binding of indapamide to plasma proteins is 79%.
The plasma elimination half-life is 14 to 24 hours (mean 18 hours).
Steady state is achieved after 7 days.
Repeated administration does not lead to accumulation.

Metabolism:
Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites.

High risk individuals:
Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, *i.e*. bradypnoea and peripheral vasodilation.
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:
Silica, colloidal anhydrous
Hypromellose
Lactose monohydrate
Magnesium stearate
Povidone

Film-coating:
Glycerol
Hypromellose
Macrogol 6000
Magnesium stearate
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store below 30° C.

6.5 Nature and contents of container

Blister pack of 30 tablets contained in an overlabelled outer cardboard carton.

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 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 Parallel Product Authorisation Number

PPA 465/219/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 2009

10 DATE OF REVISION OF THE TEXT