SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide Tablets 2.5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Indapamide Ph Eur as indapamide hemihydrate 2.5 mg.

3 PHARMACEUTICAL FORM

Coated tablets.

Appearance: white, circular, biconvex, sugar-coated tablet printed with the company logo or printed with ‘I’

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of essential hypertension.

4.2 Posology and Method of administration

Adults:
The dosage of one tablet, containing 2.5mg indapamide, to be taken daily in the morning. The action of indapamide is progressive and the reduction in blood pressure may continue and not reach a maximum until several months after the start of therapy. A larger dose than 2.5mg of indapamide daily is not recommended as there is no appreciable additional anti-hypertensive effect but a diuretic effect may become apparent. If a single daily tablet of indapamide does not achieve a sufficient reduction in blood pressure, another anti-hypertensive agent may be added such as beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents.

Children:
There is no experience of the use of this drug in children.

Administration:
Route of administration: Oral.
4.3 Contra-indications

Severe renal failure.
Hepatic encephalopathy or severe impairment of liver function.
Hypokalaemia.
Hypersensitivity to sulphonamides.
Hypersensitivity to the active ingredient or any of the excipients.
Recent cerebrovascular accident

4.4 Special Warnings And Precautions For Use

Warnings:
When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic must be stopped immediately if this occurs or there are signs of increasing renal insufficiency.

A slight weight loss has been reported in some patients taking indapamide.

Precautions:
-Water and electrolyte balance:

Plasma Sodium:
This must be measured before starting treatment, then at regular intervals subsequently. Any diuretics 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 Adverse reactions and Overdose sections).

Plasma Potassium:
Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. The risk of onset of hypokalaemia (< 3.4mmol/l) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or poly-medicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients.
In this latter 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 pre-disposing 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. 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/ml, 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 pre-existing renal insufficiency.

-Athletes:
The attention of athletes is drawn to the fact that this drug contains an active ingredient which may give a positive reaction in doping tests.

There is no evidence of rebound hypertension on withdrawal of indapamide.

4.5 Interaction with other medicinal products and other forms of interaction

When indapamide is used in conjunction with carbenoxolone or diuretics such as bumetanide, frusemide, piretanide, thiazides and xipamide, hypokalaemia may result. The co-administration of indapamide with diuretics which may cause hypokalaemia is not recommended. At doses higher than recommended, indapamide has a diuretic effect, therefore it is not recommended for prescription with a diuretic agent which may cause hypokalaemia. No interactions have been reported between indapamide and oral hypoglycaemic agents, anti-coagulants and uricosurics.

If hypokalaemia occurs, the action of digoxin can be potentiated.

Inadvisable combinations:

-Lithium:
Increased plasma lithium with signs of overdose, 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.

Long term treatment with this type of diuretic may reduce excretion of lithium.

**Non-antiarrhythmic drugs prolonging the QT interval or causing torsade de pointes** (astemizol, IV-erythromycin, halofantrine, pentamidine, sultopride, terfenadine, vincamine):

Torsade de pointes (hypokalaemia is a predisposing factor, the same applying to bradycardia and a pre-existing long QT interval).

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

**Combinations requiring precautions**

**Antiarrhythmic agents causing torsade de pointes:** Group 1a antiarrhythmic drugs (quinidine, hydroquinidine, disopyramide), amiodarone, bretylium, sotalol:

Torsade de pointes (hypokalaemia is a predisposing factor, the same applying to bradycardia and a pre-existing long QT interval).

Prevention of hypokalaemia and, if necessary, correction; monitoring of QT interval. In cases of torsade de pointes, do not give antiarrhythmic drugs (management by pacemaker).

**Digitalis preparations:**

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

**N.S.A.I.Ds. (systemic), high dose salicylates:**

Possible decrease in antihypertensive effect of indapamide.

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 a converting enzyme inhibitor is started in the presence of pre-existing sodium depletion (in particular in individuals 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 only gradually. In congestive cardiac failure, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the combined 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 mineralocorticoids (systemic), 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.

Combinations which must be taken into consideration:

**Potassium-sparing diuretics (amiloride, spironolactone, triamterene):**
Such rational combinations, useful in certain patients, do not eliminate the possibility of hypokalaemia or, in particular in renal failure and diabetic patients, of hyperkalaemia.
Monitor plasma potassium, ECG if required and adjust treatment if necessary.

**Metformin:**
In the presence of functional renal insufficiency related to diuretics and more particularly to loop diuretics, increased risk of metformin induced lactic acidosis. Do not use metformin when plasma creatinine exceeds 15mg/litre (135μmol/litre) in men and 12mg/litre (110μmol/litre) 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 (tricyclics), neuroleptics:**
Antihypertensive effect and risk of orthostatic hypotensive increased (additive effect).

**Calcium salts:**
Risk of hypercalcaemia resulting from decreased urinary calcium elimination.

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

**Corticosteroids, tetracosactide (systemic):**
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.

**Breast-feeding**
Breast feeding is inadvisable, because indapamide is excreted in human milk.

4.7 Effects on Ability to Drive and Use Machines
Diuretics may cause dizziness. Occurrence of dizziness may interfere with driving.

4.8 Undesirable Effects

Frequency estimate: *Very common* (> 1/10); *Common* (> 1/100, < 1/10); *Uncommon* (> 1/1,000, < 1/100); *Rare* (> 1/10,000, < 1/1,000); *Very rare*, including isolated reports (< 1/10,000).

The majority of adverse effects concerning clinical or laboratory parameters are dose-dependent. Thiazide-related diuretics, including indapamide, may cause:

**Blood and lymphatic system:**
*Very rare:* Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.

**Nervous system / Sensory system:**
*Rare:* Vertigo, dizziness, syncope, fatigue, headache, paraesthesia, reversible acute myopia.

**Cardiovascular system:**
*Rare:* Palpitations.
*Very rare:* Arrhythmia, hypotension.

**Gastrointestinal system:**
*Rare:* Nausea, constipation, anorexia, diarrhoea, dyspepsia, dry mouth.
*Very rare:* Pancreatitis.
Liver:
In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see Contraindications and Special Warnings).
*Very rare:* Abnormal hepatic function.

Kidney:
*Rare:* Renal insufficiency.

Skin and subcutaneous tissue:
Hypersensitivity reactions, mainly neurological in subjects with a predisposition to allergic and asthmatic reactions.
*Common:* Maculopapular rashes.
*Uncommon:* Purpura.
*Rare:* Photosensitivity.

Possible worsening of pre-existing acute disseminated lupus erythematosus, erythema multiforme and epidermal necrolysis.

Musculoskeletal system:
*Rare:* Muscle cramps.

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.

Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see Special Warnings and Precautions for Use).

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.

An increase in plasma uric acid and blood glucose during treatment; a slight reduction in glucose tolerance may occur in patients with diabetes mellitus. Appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes.

*Very rare:* Hypercalcaemia.

4.9 Overdose

Expected symptoms of overdosage would be electrolyte imbalance, hypotension, gastrointestinal disturbances and muscular weakness. Treatment would be symptomatic, directed at correcting the electrolyte abnormalities and emesis or gastric lavage should be considered.
5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Indapamide is an indoline derivative of chlorsulphonamide which shares many chemical, pharmacodynamic and therapeutic similarities with other sulphonamide diuretics. In addition to its diuretic activity indapamide has been shown to decrease vascular smooth muscle reactivity and peripheral resistance in various in-vitro and in-vivo models.

5.2 **Pharmacokinetic Properties**

Indapamide is rapidly absorbed from the gastrointestinal tract. Elimination is biphasic with a terminal half-life of 14 to 18 hours. It is extensively metabolised. About 60 to 70% of the dose has been reported to be excreted in the urine; only about 5% is excreted unchanged. About 16 to 23% of administered dose is excreted in the faeces. Indapamide is about 71 to 79% bound to plasma proteins and it is preferentially taken up in the red blood cells.

5.3 **Preclinical Safety Data**

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Lactose monohydrate, maize starch, povidone, magnesium stearate.

*Sugar coat:* Opaseal (polyvinylacetate phthalate, stearic acid), talc, calcium carbonate, acacia, titanium dioxide (E171), sucrose, Opaglos 6000P (yellow carnauba wax, white beeswax, shellac).

6.2 **Incompatibilities**
6.3 Shelf-Life

3 years.

6.4 Special Precautions for Storage

Store below 25°C in a dry place.

6.5 Nature and Content of Container

Polypropylene tubes with low density polyethylene caps. High density polyethylene film may be used as packing material.

Pack sizes: 28, 30, 50, 56, 60, 100, 120 and 250 tablets.

Blister packs consisting of clear PVC and hard temper aluminium foil contained in a carton.

Pack sizes: 28, 30, 50, 56, 60 100 and 120 tablets.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road,
Clonmel,
Co. Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00790/0102
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23/06/2008

10 DATE OF REVISION OF THE TEXT

23/06/2008