SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide 2.5mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Indapamide 2.5mg equivalent to 2.5mg of indapamide hemihydrate.
Excipients: 56mg of lactose monohydrate per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of essential hypertension. Indapamide may be used as sole therapy or combined with other antihypertensive agents.

4.2 Posology and method of administration

Adults:
The dosage is 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. The co-administration of Indapamide with diuretics, which may cause hypokalaemia, is not recommended.

There is no evidence of rebound hypertension on withdrawal of indapamide.
Renal failure: (see section 4.3 & 4.4)
In severe renal failure (creatinine clearance below 30ml/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 Indapamide when renal function is normal or only minimally impaired.

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

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

Administration:
Route of administration: Oral.

4.3 Contraindications
i) Severe renal failure.
ii) Hepatic encephalopathy or severe impairment of liver function.
iii) Hypokalaemia.
iv) Hypersensitivity to Indapamide, to other sulphonamides, or to any of its excipients.

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 or there are signs of increasing renal insufficiency.

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

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 section 4.8 Undesirable effects and section 4.9 Overdose).

**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 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. 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. 220µmol/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 Interactions with other medicinal products and other forms of interaction

The concomitant administration of the following medicaments with Indapamide is not recommended:

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 is 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, sulpocrine, tiapride)
- Butyrophenones (droperidol, haloperidol)
- Others: bepridil, Cisapride, diphenamil, 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.
NSAIDs-(systemic route) including COX-2 selective inhibitors, high dose salicylic acid (≥3g/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.

ACE (Angiotensin converting enzyme) inhibitors:
Risk of sudden hypotension and/or acute renal failure when treatment with an ACE is initiated in the presence of pre-existing sodium depletion (particularly in patients with renal artery stenosis)

In hypertension, when prior diuretic treatment may have caused sodium depletion, it is necessary to:

- either stop the diuretic 3 days before starting treatment with the ACE inhibitor, and restart a hypokalaemic diuretic if necessary
- or give low initial doses of the ACE inhibitor and increase the dose gradually.

In congestive heart failure, start with a very low dose of ACE 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 ACE inhibitor

Other compounds causing hypokalaemia: Amphotericin B (IV), gluco-and-mineralocorticosteroids (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 the 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 15mg/l (135µmol/l) in men and 12mg/l (110µmol/l) in women.

**Iodinated contrast media**: In the presence of dehydration caused by diuretics, there is an 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 (addictive 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 ciclosporin levels, even in the absence of water/sodium depletion.

**Corticosteroids, tetracosactide (systemis route)**: Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 **Fertility, 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, because indapamide is excreted in human milk.

4.7 **Effects on ability to drive and use machines**

Diuretics may cause dizziness or other reactions especially in the relation to a decrease in blood pressure or at the start of the treatment or when another
antihypertensive agent is added. Occurrence of dizziness may interfere with driving.

4.8 Undesirable effects

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

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).

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

Nervous system / Sensory system:
Rare: Vertigo, fatigue, headache, paraesthesia.
Not known: syncope

Cardiac disorders:
Rare: Palpitations.
Very rare: Arrhythmia, hypotension.
Not known: Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)

Gastrointestinal disorders:
Uncommon: Vomiting
Rare: Nausea, constipation, dry mouth.
Very rare: Pancreatitis.

Hepatobiliary disorders:
Very rare: Abnormal hepatic function.
Not known: In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4), hepatitis.

Renal and urinary disorders:
Very rare: Renal failure

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.

Frequency unknown:
Possible worsening of pre-existing acute disseminated lupus erythematosus, erythema multiforme and epidermal necrolysis. Cases of photosensitivity reactions have been reported (see section 4.4).

Metabolism and nutrition disorder:
During clinical trials, hypokalaemia (plasma potassium < 3.4 mmol/l) was seen in 25% of patients and < 3.2 mmol/l in 10% of patients after 4 to 6 weeks of treatment. After 12 weeks of treatment, the mean fall in plasma potassium was 0.41 mmol/l.
Very Rare: Hypercalcaemia

Frequency 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.

Investigations:
Not known:
• Electrocardiogram QT prolonged (see section 4.4 and 4.5)

• 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.

• Elevated liver enzyme levels.

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 the yellow card scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Indapamide has been found free of toxicity at up to 40mg, i.e. 16 times the therapeutic dose.
Signs of acute poisoning take the form above all 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 washout 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

ATC code C03BA11 Pharmacotherapeutic group: Sulphonamides, plain.

Indapamide is a non-thiazide sulphonamide with an indole ring, belonging to the diuretic family. At the dose of 2.5mg per day of Indapamide exerts a prolonged antihypertensive activity in hypertensive human subjects.

Dose-effect studies have demonstrated that, at the dose of 2.5mg per day, the antihypertensive effect is maximal and the diuretic effect is sub-clinical. As this antihypertensive dose of 2.5mg per day, Indapamide reduces vascular hyper reactivity to noradrenaline in hypertensive patients and decreases total peripheral resistance and arteriolar resistance.

The implication of an extrarenal mechanism of action in the antihypertensive effect is demonstrated by maintenance of its antihypertensive efficacy in functionally anephric hypertensive patients.

The vascular mechanism of action of Indapamide involves:
- A reduction in the contractility of vascular smooth muscle due to a modification of transmembrane ion exchanges, essentially calcium.
- Vasodilation due to stimulation of the synthesis of prostaglandin PGE$_2$ and the vasodilator and platelet antiaggregant prostacyclin PGI$_2$.
- Potentiation of the vasodilator action of bradykinin.

It has also been demonstrated that in the short-, medium- and long term, in hypertensive patients, Indapamide:
- Reduces left ventricular hypertrophy
- Does not appear to alter lipid metabolism: triglycerides, LDL-cholesterol & HDL cholesterol;
- Does not appear to alter glucose metabolism, even in diabetic hypertensive patients. Normalisation of blood pressure and a significant reduction in microalbuminuria have been observed after prolonged administration of Indapamide in diabetic hypertensive subjects.

The co-prescription of Indapamide with other antihypertensives (beta-blockers, calcium channel blockers or angiotensin converting enzyme inhibitors) results in improved control of hypertension with an increased percentage of responders compared to that observed with single-agent therapy.

5.2 Pharmacokinetic properties
Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Peak blood levels are obtained after 1 to 2 hours. Indapamide is concentrated in the erythrocytes and is 79% bound to plasma protein and to erythrocytes. It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility. 70% of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is metabolised to a marked degree with 7% of the unchanged product found in the urine during the 48 hours following administration. Elimination half-life (β phase) of indapamide is approximately 15-18 hours.

5.3 Preclinical safety data
Indapamide has been tested negative concerning mutagenic and carcinogenic properties. No findings in the preclinical testing, which could be of relevance for the prescriber.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet Core:
Lactose Monohydrate
Maize Starch
Povidone
Magnesium Stearate

Tablet Coating:
Opaseal varnish
Purified tale,
Calcium Carbonate,
Acacia,
Titanium Dioxide (171)
Sucrose,
Opaglos 6000P.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C in the original package to protect from moisture.

6.5 Nature and contents of container
1. 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.

2. 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY HOLDER
Athlone Pharmaceuticals
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORITY NUMBER(S)
PL 30464/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/06/2010
10 DATE OF REVISION OF THE TEXT

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