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The Medicines and Healthcare products Regulatory Agency (MHRA) granted Athlone Pharmaceuticals a Marketing Authorisation (licence) for the medicinal product, Indapamide 2.5mg tablets (PL 30464/0030), on 17th June 2010. This is a prescription-only medicine (POM).

Indapamide is one of a group of medicines called anti-hypertensives. It is a diuretic. It acts on the kidneys to remove more water from the body, thereby increasing the volume of urine. It reduces blood pressure by reducing the volume of blood and the work required by the heart. Indapamide is used to treat high blood pressure (hypertension).

This application is identical to a previously granted licence for Indapamide Tablets 2.5mg (PL 00790/0102), authorised to Clonmel Healthcare Limited on 2nd November 1993. The proposed and reference products are identical.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Indapamide 2.5mg tablets outweigh the risk; hence a Marketing Authorisation has been granted.
INDAPAMIDE 2.5MG TABLETS
(INDAPAMIDE)
PL 30464/0030

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Athlone Pharmaceuticals a Marketing Authorisation for the medicinal product Indapamide 2.5mg tablets (PL 30464/0030) on 17th June 2010. The product is a prescription-only medicine.

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing Indapamide Tablets 2.5mg (PL 00790/0102), licensed to Clonmel Healthcare Limited on 2nd November 1993.

Indapamide 2.5mg tablets are indicated for the treatment of essential hypertension. Indapamide may be used as sole therapy or combined with other antihypertensive agents.

Indapamide is a non-thiazide sulphonamide with an indole ring, belonging to the diuretic family. At the dose of 2.5mg per day, 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. At 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.

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.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Athlone Pharmaceuticals’ marketing of Indapamide 2.5mg tablets, an identical product to one already on the market, is not predicted to result in an overall increase in the environmental exposure concentrations of the active ingredient, indapamide.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.
PHARMACEUTICAL ASSESSMENT

LICENCE NUMBER: PL 30464/0030

PROPRIETARY NAME: Indapamide 2.5mg tablets

ACTIVE INGREDIENT/S: Indapamide

COMPANY NAME: Athlone Pharmaceuticals

E.C. ARTICLE: Article 10c of Directive 2001/83/EC (as amended)

LEGAL STATUS: POM

1. INTRODUCTION

This is a simple abridged application, submitted under Article 10c of Directive 2001/83/EC (as amended) for Indapamide 2.5mg tablets. The proposed Marketing Authorisation Holder (MAH) is Athlone Pharmaceuticals, Ballymurray, Co. Roscommon, Ireland.

The reference product is Indapamide Tablets 2.5mg (PL 00790/0102), authorised to Clonmel Healthcare Limited on 2nd November 1993. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved name of the product is Indapamide 2.5mg tablets. The product has been named in line with current requirements and the product name is acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Indapamide 2.5mg tablets are presented as white, circular, coated tablets for oral administration. Each tablet contains 2.5 mg of the active ingredient, indapamide. The tablets are licensed for marketing in the following containers (full details are provided in the SmPC):

i) Polypropylene tubes with low density polyethylene caps - pack sizes: 28, 30, 50, 56, 60, 100, 120 and 250 tablets

ii) 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

The MAH has stated that not all pack sizes may be marketed.

The approved shelf-life (3 years) and storage conditions (‘Store below 25°C in the original package to protect from moisture’) are consistent with the details registered for the cross-reference product.

2.3 Legal status

POM - The product is available by supply through pharmacies, subject to a medical prescription.
2.4 Marketing Authorisation Holder / Contact Persons / Company
The proposed Marketing Authorisation Holder is ‘Athlone Pharmaceuticals, Ballymurray, Co. Roscommon, Ireland’.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers
The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is identical to the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product / shelf-life specification
The proposed finished product specification is consistent with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
The only excipients used that contain material of animal or human origin are magnesium stearate and lactose monohydrate. Appropriate documentation has been provided for these excipients confirming their suitability for inclusion in the finished product. A European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP) has been provided for magnesium stearate confirming that it meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. For lactose monohydrate, the applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product (white, circular, coated tablets, printed “I”) is identical to that of the cross-reference product.
5. **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**

The approved SmPC is consistent with the details registered for the cross-reference product, as well as the SmPC of the innovator product, Natrilix 2.5 mg Tablets (PL 00093/0022, Servier Laboratories Ltd).

6. **PATIENT INFORMATION LEAFLET (PIL) / CARTON**

**PIL**

The approved PIL is satisfactory and in line with the approved SmPC. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the details registered for the cross-reference product.

PIL user testing has been accepted, based on a bridging report provided by the applicant making reference to the PILs for Furosemide 20, 40 and 50 mg/ml Oral Solution, Furosemide 20 mg and 40 mg Tablets (in-house PIL), and for the innovator product, Natrilix 2.5 mg Tablets (PL 00093/0022, Servier Laboratories Ltd). The structure and content of the daughter PIL (Indapamide 2.5 mg tablets) is very similar to that of the 3 parent PILs and the key safety messages are the same. Font, colour, style and size are very similar for the daughter PIL and the in-house PIL for Furosemide 20 mg and 40 mg Tablets. The bridging report is accepted.

**Cartons**

Colour mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation the applicant has included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. However, they have committed to submitting mock-ups for currently unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

7. **CONCLUSIONS**

The grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.
NON CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended).

No new clinical data have been supplied with the application, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

Efficacy
Medicinal products containing indapamide have been available in the UK for more than ten years. Their use is well-established, with recognised efficacy and acceptable safety.

This application is considered identical to the previously granted application for Indapamide Tablets 2.5mg (PL 00790/0102, Clonmel Healthcare Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with the details registered for the cross-reference product, as well as the SmPC of the innovator product, Natrilix 2.5 mg Tablets (PL 00093/0022, Servier Laboratories Ltd).

The approved PIL text is satisfactory and in line with the approved SmPC. It is consistent with the details registered for the cross-reference product. PIL user testing has been accepted, based on a bridging report provided by the applicant making reference to the PILs for Furosemide 20, 40 and 50 mg/ml Oral Solution, Furosemide 20 mg and 40 mg Tablets (in-house PIL), and for the innovator product, Natrilix 2.5 mg Tablets (PL 00093/0022, Servier Laboratories Ltd). The bridging report is accepted.

Colour mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements. The MAH has stated that not all licensed pack sizes may be marketed. However, they have committed to submitting mock-ups for currently unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with indapamide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is, therefore, considered to be positive.
INDAPAMIDE 2.5MG TABLETS
(INDAPAMIDE)
PL 30464/0030

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 2nd August 2007

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 14th August 2007


5. The application was determined on 17th June 2010
INDAPAMIDE 2.5MG TABLETS
(INDAPAMIDE)
PL 30464/0030

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Indapamide 2.5mg tablets is as follows:

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

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 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. 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
- Class III antiarrhythmics
- Some antipsychotics
- Phenothiazines
- Benzamides
- Butyrophenones
- Others: bepridil, cisapride, diphenamid, 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
- 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-mineralocorticoids (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 15g/l (135µmol/l) in men and 12mg/l (110µmol/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 (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-
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 foeto-placental 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 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 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:

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.

Cardiac disorders:
Rare: Palpitations.
Very rare: Arrhythmias, hypotension.

Gastrointestinal system:
Uncommon: vomiting
Rare: Nausea, constipation, dry mouth.
Very rare: Pancreatitis.

Hepatobiliary disorders:
Very rare: Abnormal hepatic function. In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see Contraindications and Special Warnings).

Renal and urinary disorders:
Very rare: Renal failure.

Skin and subcutaneous tissue:
Common: Maculopapular rashes.
Uncommon: Purpura.
Very Rare: Angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome.
Frequency unknown: Hypersensitivity reactions, mainly dermatological in subjects with a predisposition to allergic and asthmatic reactions.

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).

**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 of treatment. After 12 weeks of treatment, the mean fall in plasma potassium was 0.23 mmol/l.

Very Rare: Hypercalcaemia

Frequency not known:
- 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.

### 4.9 Overdose

Indapamide has been found free of toxicity at up to 40mg, i.e. 27 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 PGE₂ and the vasodilator and platelet antiaggregant prostacyclin PGI₂.

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 talc
- 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 AUTHORISATION HOLDER

Athyone Pharmaceuticals
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30464/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/06/2010

10 DATE OF REVISION OF THE TEXT

17/06/2010
UKPAR Indapamide 2.5mg Tablets

PATIENT INFORMATION LEAFLET

INPADAMME 2.5mg TABLETS

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in the leaflet, please tell your doctor or pharmacist.

1. WHAT INDAPAMIDE 2.5mg TABLETS ARE AND WHAT THEY ARE USED FOR
Indapamide is one of a group of medicines called anti-hypertensives. Indapamide is a diuretic. It acts on the kidneys to remove more water from the body, thereby increasing the volume of urine. It reduces blood pressure by reducing the volume of the blood and the work required by the heart.
Indapamide is used to treat high blood pressure (hypertension).

2. BEFORE YOU TAKE INDAPAMIDE 2.5mg TABLETS
Do not take indapamide 2.5mg Tablets if you have:
- An allergy (hypersensitivity) to indapamide or any of the other ingredients of Indapamide 2.5mg Tablets
- Are allergic (hypersensitive) to sulphonamides (e.g. co-trimoxazole, used to treat infections)
- A severe kidney disease
- A severe liver disease or suffer from a condition called hepatic Encephalopathy (liver problems which affect the brain and central nervous system)
- Been told that you have low levels of potassium in your blood (hypokalaemia) which may cause muscle weakness or paralysis.

Take special care with Indapamide 2.5mg Tablets:
Tell your doctor if you:
- Have recently suffered a stroke
- Are pregnant, planning to become pregnant or are breast-feeding
- Are diabetic
- Suffer from gout
- Have very low levels of sodium in your blood, which may be caused by excessive sweating, vomiting or reaction to another drug
- Need to have a test to check how well your parathyroid gland is working
- Have any heart rhythm problems such as irregular heartbeat
You should tell your doctor if you have had photosensitivity reactions or are to expose your skin to UVA light or the sun.
You should visit your doctor regularly while you are taking this medicine, as he/she may wish to carry out some tests to check for low sodium or potassium levels or high calcium levels.

Athletes: This drug contains an active ingredient that may give a positive reaction in doping tests.

Taking other medicines:
Please tell your doctor if you have taken or are taking any other medicines, even those obtained without a prescription or herbal medicines.
You should NOT take Indapamide with Lithium, used to treat depression due to the risk of increased levels of lithium in the blood.
You should consult your doctor BEFORE taking any other medicines, especially the following:
- Medicines used to treat an abnormal heartbeat such as quinidine or carbamazepine (e.g. Dilgxin, hydroquinidine, disopyramide, amiodarone, ibutilide, dofetilide)
- Digitalis preparations (e.g. digoxin, digitoxin) used to treat heart failure
- ACE inhibitors - angiotensin converting enzyme inhibitors (e.g. captopril), used in the treatment of high blood pressure
- Potassium sparing diuretics (e.g. amiloride, spironolactone, triamterene), which increase the flow of urine without excessive loss of potassium
- Septiflex, used to treat angina pectoris, a condition causing chest pain
- Captopril, used to treat reduced movement of the gut and stomach and bowel constipation
- Carbamoxone, dexamethasone, used in the treatment of ulcers
- Chloroquine (e.g. buparlamide, furamamide, pentamidine, thiazides or oxapamide), that are used to increase the flow of urine
- Aminoglutethimide or mitolactol (anti-estrogens), intravenous erythromycin, sparfloxacin, moxifloxacin (antibiotics), halotestin (anti-male sex drug)
- Pentamidine, used to treat certain types of pneumonia
- Salsalate, used to treat muscle stiffness occurring in diseases such as multiple sclerosis
- NSAIDs - non-steroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen) used in the management of arthritis
- Amphotericin B used to treat fungal infections
- Stimulant laxatives, which are used for constipation
- Metformin, used in the treatment of diabetes
- Anti-depressants and neuroleptics e.g. sulpiride, trifluoroantidepressants, antipsychotic drugs used to treat mental disorders such as depression, anxiety, schizophrenia
- Calcium tablets or supplements
- Clozapine, benzoil fluoride or other medicines to depress the immune system after organ transplantation, to treat autoimmune diseases or severe rheumatic or skin diseases
- Corticosteroids used to reduce inflammation, treatment of severe asthma and rheumatoid arthritis
- Trenace to treat Crohn’s disease.

Tell your doctor if you need to have tests requiring administration of iodinated contrast media

Pregnancy and breast-feeding:
Do not take this medicine without consulting your doctor if you are pregnant, planning to become pregnant or are breast-feeding. This medicine is not recommended during pregnancy or while breast-feeding.

Driving and using machines:
As this medicine may make you feel dizzy, you should not drive or operate machinery until you know how the drug affects you.

Important information about some of the ingredients of Indapamide:
These tablets contain Lactose Monohydrate. If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE INDAPAMIDE 2.5mg TABLETS
Always take indapamide 2.5mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist, if you are not sure.

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Adults only:
The usual dose is one tablet to be taken in the morning.

Children and adolescents (<18 years of age):
Indapamide 2.5mg tablets are not recommended for use in children or adolescents.

How to take Indapamide 2.5mg Tablets:
You should take your tablets in the morning before breakfast. The tablets should be swallowed with water.

If you take more Indapamide 2.5mg Tablets than you should:
If you or anybody else has taken too many tablets you should contact your nearest hospital casualty department or doctor immediately. A very large dose of Indapamide 2.5mg Tablets can cause nausea (feeling sick), vomiting, low blood pressure, cramps, dizziness, drowsiness, confusion and changes in the amount of urine produced by the kidneys.

If you forget to take Indapamide 2.5mg Tablets:
If you forget to take a dose, take the next dose as soon as you remember, then go on as before. If you miss a day, do not take a double dose the following day, but continue as prescribed by your doctor. Do not take a double dose to make up for the forgotten dose.

If you stop taking Indapamide 2.5mg Tablets:
As the treatment for high blood pressure is usually long-term, you should discuss with your doctor before stopping this medicinal product.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Indapamide 2.5mg Tablets can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of the following:

• Common (less than 1 patient in 10 but more than 1 in 100):
  - Low potassium in the blood, which may cause muscle weakness, red raised skin rash.

• Uncommon (less than 1 patient in 100 but more than 1 in 1000):
  - Vomiting, red or purple spots beneath the skin (Purpura).

• Rare (less than 1 in 1000 but more than 1 in 10,000):
  - Nausea, constipation, dry mouth, vertigo (dizziness due to an imbalance in the ear), tiredness and headache.
  - Pins and needles or tingling sensation of the skin.
  - Increased risk of dehydration in the elderly and in patients suffering from heart failure.
  - Feeling of the heart pounding (palpitations).

• Very rare (less than 1 in 10,000):
  - An increase in uric acid or glucose in the blood. A slight reduction in glucose tolerance in patients with diabetes.
  - A change in acidity of the blood.
  - Irregular heart rhythm, low blood pressure.
  - Kidney disorders causing symptoms of tiredness, increased need to urinate, itchy skin, feeling sick, swollen extremities.
  - Pancreatitis, an inflammation of the pancreas, usually marked by abdominal pain, often radiating to the back, nausea and vomiting.
  - Abnormal liver function with yellowing of the skin (symptoms such as tiredness, loss of appetite, feeling or being sick, swollen extremities). In cases of liver failure, there is a possibility of getting hepatic Encephalopathy (liver problems which affect the brain and central nervous system).
  - Changes in blood cells, such as thrombocytopenia (decrease in the number of platelets which causes easy bruising and nasal bleeding), leucopenia (decrease of white blood cells which may cause unexplained fever, soreness of the throat or other flu-like symptoms).
  - An increase in red blood cells.
  - Angioedema and/or urticaria, with swelling of the skin around the eyes, lips, hands or feet. It may cause swelling of the throat, tongue and always resulting in shortness of breath or difficulty in swallowing.
  - A severe blistering rash where layers of skin peel off leaving scalded skin. You may also have a fever. This could be an illness called ‘Toxic Epidermal Necrolysis’.
  - A skin rash with dark circles and pale centers, red patches, blistering or peeling. You may also have a fever. This could be an illness called ‘Erythema multiforme’ or ‘Steven-Johnson syndrome’.

Frequency Unknown:
If you suffer from systemic lupus erythematosus (a disorder of the immune system leading to inflammation and damage to the joints, tendons and organs), this might get worse. Cases of photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA have also been reported.

Some changes to your blood may occur. Your doctor may want to give you a blood test to check your condition. The following changes in your blood test results may occur:

• Low potassium in the blood.
• Low sodium in the blood that may lead to dehydration and low blood pressure.
• Increase in uric acid, a substance that may cause or worsen gout (painful joints especially in the feet).
• Increase in blood glucose levels in diabetic patients.
• Increase in calcium levels in the blood.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please let your doctor or pharmacist.

5. HOW TO STORE INDAPAMIDE 2.5mg TABLETS

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Store below 25°C in the original package to protect from moisture.

Do not use after the expiry date shown on the label.

Return any left over tablets to your pharmacist. Only keep them if your doctor tells you to. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

These measures will help to protect the environment.

6. FURTHER INFORMATION

What Indapamide 2.5mg Tablets contain:
Indapamide 2.5mg Tablets contain the active ingredient indapamide (as hemihydrate).

The tablet core also contains lactose monohydrate, maize starch, povidone, magnesium stearate.

The tablet coating contains Opales IS varnish, purified talc, calcium carbonate, acacia, sucrose, titanium dioxide (E171), Opacig 600P.

What Indapamide 2.5mg Tablets look like and contents of the pack:
Indapamide 2.5mg tablets are white, circular, coated tablets printed “I”. Each tablet contains 2.5mg of indapamide equivalent to 2.5mg Indapamide hemihydrate, the active ingredient.

Pack sizes: 28, 30, 50, 55, 100, 120 and 250 tablets. Not all pack sizes may be marketed.


Marketing Authorisation number: PL 30464/0030

Distributed by: Kent Pharmaceuticals Limited, Wotton Road, Ashford, Kent, TN23 6LL, U.K.

Date leaflet last revised: March 2010.
UKPAR Indapamide 2.5mg Tablets

PL 30464/0030

LABELLING

Carton – pack size 28

Indapamide 2.5mg Tablets Each tablet contains Indapamide 2.5mg (equivalent to 2.5mg of Indapamide hemihydrate). Contains lactose monohydrate. See leaflet for further information. Coated tablets for oral use. Use as directed by a physician. Please read the enclosed leaflet carefully before taking this medicine. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Store below 25°C in the original package to protect from moisture.

MA holder: Athlone Pharmaceuticals Ltd, Ballymurray, Co. Roscommon, Ireland PL 30464/0030

Distributed By: Kent Pharmaceuticals Limited, Wotton Road, Ashford, Kent, TN23 6LL, U.K.

POM

28 Coated Tablets

Barcode
Indapamide 2.5mg Tablets Each tablet contains indapamide 2.5mg equivalent to 2.3 mg of indapamide hemihydrate. Contains lactose monohydrate.

See leaflet for further information. Coated tablets for oral use. Use as directed by a physician. Please read the enclosed leaflet carefully before taking this medicine. Keep out of the reach and sight of children. Store below 25°C in the original package to protect from moisture.

MA holder: Athlone Pharmaceuticals Ltd., Ballymurray, Co. Roscommon, Ireland

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Indapamide 2.5mg Tablets

56 Coated Tablets

Blister foil