SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide Hemihydrate 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of Indapamide Hemihydrate.

Excipients with known effect:
Lactose
Sucrose
Ponceau 4R (E124)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Pink sugar-coated tablets.

4.1 Therapeutic indications

Indapamide Tablets are indicated for the treatment of essential hypertension in adults.

4.2 Posology and method of administration

For oral administration.

Posology

Adults:
The dosage is one tablet, containing 2.5mg indapamide hemihydrate, daily to be taken in the morning. The action of indapamide is progressive and the reduction in blood pressure may reach a maximum until several months after the start of therapy.
A larger dose than 2.5mg daily is not recommended as there is no appreciable additional antihypertensive effect, but a diuretic effect may become apparent.

If one indapamide tablet daily does not achieve a sufficient reduction in blood pressure, another antihypertensive agent may be added; those which have been used in combination with indapamide include beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents. Co- administration of indapamide with diuretics may cause hypokalaemia and, therefore, is not recommended.

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

Special populations

Renal impairment (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.

Hepatic impairment (see sections 4.3 and 4.4):

In severe hepatic impairment, treatment is contraindicated.

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 Tablets when renal function is normal or only minimally impaired.

Paediatric population:
The safety and efficacy of Indapamide Tablets 2.5mg in children and adolescents have not been established. No data are available.

Method of administration:
Oral use.

4.3 Contraindications

Indapamide is contraindicated in patients with:

- Hypersensitivity to the active substance, to other sulfonamides or to any of the excipients listed in section 6.1
- 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, particularly in case of electrolyte imbalance. hepatic encephalopathy which can progress to hepatic coma.
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.

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

Sucrose:
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium:
This medicine contains less than 1mmol (23mg) of sodium in each tablet, that is to say essentially sodium-free.

Special precautions for use

- **Water and electrolyte balance:**

• Plasma sodium:
This must be measured before starting treatment, then at regular intervals subsequently. 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). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be 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.

• Plasma potassium:

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. 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. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

• Plasma magnesium:

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

• 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.

- **Choroidal effusion, acute myopia and secondary angle-closure glaucoma:**

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

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 such as but not limited to:

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

phenothiazines (e.g. chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),

benzamides (e.g. amisulpride, sulpiride, sultopride, tiapride)

butyrophenones (e.g. droperidol, haloperidol)

other antipsychotics (e.g. pimozide),

other substances: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV, methadone, astemizole, terfenadine. 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. inhibitor 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:

- 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 and/or hypomagnesaemia predispose to the toxic effects of digitalis.
Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

Combinations requiring special care:

Allopurinol:

Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

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 Fertility, pregnancy and lactation

Pregnancy:
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Indapamide during pregnancy.

Breast-feeding:
Indapamide is excreted in human milk in small amounts. Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.

Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decreased or even suppression of milk lactation.

Indapamide should not be used during breast-feeding.

Fertility:
Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3). No effects on human fertility are anticipated.

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

Summary of safety profile
The most commonly reported adverse reactions are hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

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), frequency not known (cannot be estimated from the available data).

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

Metabolism and nutrition disorders:
Rare: Hypochloraemia, Hypomagnesaemia
Very Rare: hypercalcaemia
Common: Hypokalaemia (see section 4.4)
Uncommon: Hyponatraemia (see section 4.4)

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

Nervous system disorders:
Rare: vertigo, fatigue, headache, paresthesia
Not known: Syncope

Eye disorders:
Not known: Choroidal effusion, Myopia, Blurred vision, Visual impairment, Acute angle-closure glaucoma

Cardiac disorders:
Very rare: arrhythmia,
Not known: Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)

Vascular Disorders:
Very rare: Hypotension

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

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), Hepatitis.

Skin and subcutaneous tissue disorders:
Common: maculopapular rashes, hypersensitivity reactions
Uncommon: purpura
Very rare: Angioedema, urticaria, toxic epidermal necrolysis, Steven Johnson syndrome, Not known: Possible worsening of pre-existing acute disseminated lupus erythematosus, Photosensitivity reactions (see section 4.4)

Renal and urinary disorders:
Very rare: renal failure.

Musculoskeletal and Connective Tissue Disorders:
Not known: Muscle spasms, Muscular weakness, Myalgia, Rhabdomyolysis

Investigations:
Not known: Electrocardiogram QT prolonged (see sections 4.4 and 4.5), Blood glucose increased (see section 4.4), blood uric acid increased (see section 4.4), elevated liver enzyme levels

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:
- Indapamide 1.5mg: 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.
- Indapamide 2.5 mg: 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 treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l

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, or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Indapamide has been found free of toxicity at up to 40 mg, i.e. 16 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).

Management

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: C03BA11

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

Pharmacodynamic effects
Dose-effect studies have demonstrated that, at the dose of 2.5 mg per day, the antihypertensive effect is maximal and the diuretic is mild intensity.

At this antihypertensive dose of 2.5 mg per day, Indapamide Tablets reduces vascular hyperreactivity 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 Tablets involves:

• a reduction in the contractility of vascular smooth muscle due to a modification of transmembrane ion exchanges, essentially calcium;

• vasodilatation 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 Tablets:

• reduces left ventricular hypertrophy;

• does not appear to alter lipid metabolism: triglycerides, LDL-cholesterol and 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 Tablets in diabetic hypertensive subjects.

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

5.2 Pharmacokinetic properties

Absorption
Indapamide is rapidly and completely absorbed from the gastro-intestinal tract. Peak blood levels are obtained after 1 to 2 hours.

Distribution
The drug is preferentially and reversibly taken up by red blood cells and is about 79% bound to plasma proteins and to erythrocytes. It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility.

Metabolism
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.

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.

Reproductive toxicity studies have not shown embryotoxicity and teratogenicity. Fertility was not impaired either in male or in female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:
Lactose
Di-basic Calcium Phosphate
Maize Starch
Magnesium Stearate
Croscarmellose Sodium

Tablet coating:
Opalux pink AS-F-1312 contains sucrose, titanium dioxide (E171), Talc, Ponceau 4R Aluminum lake (E124), Erythosine aluminum lake (E127), povidone (E1201) and sodium benzoate (E211)
Sugar Syrup 70% (Purified water and Sucrose)
Purified talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Protect from light.
Do not store above 25ºC.

6.5 Nature and contents of container

Blister packs which consist of strips made from hard PVC/PVdC with a foil lid.
Pack sizes 28 tablets in blister packs of 14 (2 x 14); 30 tablets in blister packs of 15 (2 x 15); 56 tablets in blister packs of 14(4 x 14) and 60 tablets in blister packs of 15 (4 x 15).

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill,
Basingstoke, RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0315

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10 DATE OF REVISION OF THE TEXT

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