SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indapamide 2.5mg

Excipient(s) with known effect

Lactose

Sucrose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

White, 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

Posology

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; those which have been used in combination with indapamide include 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.

Special populations

Renal failure (see sections 4.3 and 4.4):

In severe renal failure (creatinine clearance below 30ml/min), treatment is contraindicated.

Thiazides 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 when renal function is normal or only minimally impaired.

Paediatric population:

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

Method administration

Oral use.

4.3 Contraindications

Hypersensitivity to the active substance, or 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

Porphyria

Addison's disease

Refractory hypokalaemia, hyponatraemia, hypercalcaemia

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 a 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 from the sun or artificial UVA.

Excipients

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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. 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. The risk of onset of hypokalaemia (<3.4mmol/l) must be prevented in certain high-risk populations, i.e. the elderly, malnourished and/or polymedicated, patients with hyperaldosteronism, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

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

fatal torsades de pointes.

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

Plasma calcium

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment should be withdrawn before the investigation of parathyroid function.

Blood glucose

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

Uric acid

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25mg/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. Use with caution in patients with nephrotic syndrome.

Athletes

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

Indapamide may cause exacerbation of systemic lupus erythematosus.

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

Torsade de pointes-inducing drugs:

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide, flecainide)
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics:
    - phenothiazines (chlorpromazine, cyamenazine, levomepromazine, thioridazine, trifluoperazine),
    - benzamides (amisulpride, sulpiride, tiapride),
    - butyrophenones (droperidol, haloperidol),
    - Others: pimozide
- Others: bepridil, cisapride, diphemanil, erythromycin IV, clarithromycin, 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 (≥ 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 (ACE) inhibitors:

Risk of sudden hypotension and/or acute renal failure when treatment with an

ACE 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 ACE inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the ACE inhibitor and increase only 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, reboxetine and theophylline:

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

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

Digitalis preparations:

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

Combinations which must be taken into consideration:

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

Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia particularly in patients with renal failure or diabetes 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, 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 circulation ciclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route):

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

Antihypertensive agents and other compound causing hypotension (see also ACE inhibitors):

Enhanced antihypertensive effect may occur and the risk of orthostatic hypotension may be increased (additive effect) with other antihypertensive agents (e.g. adrenergic neurone blockers, alpha-adrenoceptor blocking drugs, beta-blockers, calcium channel blockers, nitrates, vasodilator antihypertensive drug, clonidine, methyldopa, moxonidine),

There is an increased risk of first dose hypotension with post-synaptic alpha-blockers such as prazosin.

Enhanced hypotensive effects may also occur with other drugs which cause reductions in blood pressure (e.g. general anaesthetics, anxiolytics and hypnotics, neuroleptics, tricyclic antidepressants, mono-amine oxidase inhibitors, alprostadil, levodopa).

Agents affecting blood calcium levels

Risk of hypercalcaemia is increased with concomitant use of indapamide and calcium salts, vitamin D or toremifene.

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

There is insufficient information on the excretion of indapamide/metabolites in human milk. 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 or to operate machinery may be impaired.

4.8 Undesirable effects

Summary of safety profile

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

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 treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

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

Tabulated summary of adverse reactions

The following undesirable effects have been observed with indapamide during treatment ranked under the following frequency:
Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000), very rare (< 1/10,000) and frequency not known (cannot be estimated from the data available).

Body System	Frequency	Adverse Event

Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Metabolism and nutrition disorders	Very rare	Hypercalcaemia
	Not known	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4) Hyponatraemia (see section 4.4)
Nervous system disorders	Rare	Vertigo, fatigue, headache, paraesthesia
	Not known	Syncope
Eye disorders	Not known	Visual impairment, myopia, blurred vision
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	Nausea, constipation, dry mouth
	Very rare	Pancreatitis
Hepatobiliary disorders	Very rare	Abnormal hepatic function
	Not known	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see section 4.3 and 4.4) Hepatitis
Skin and subcutaneous tissue disorders	Common	Hypersensitivity reactions Maculopapular rashes
	Uncommon	Purpura
	Very rare	Angioedema, urticaria, toxic epidermal necrolysis, Stevens-Johnson Syndrome
	Not known	Possible worsening of pre-existing acute disseminated lupus erythematous Photosensitivity reactions (see section 4.4)

Musculoskeletal and connective tissue disorders	Not known	Muscle cramps
Renal and urinary disorders	Very rare	Renal failure
Reproductive system and breast disorders	Not known	Impotence
General disorders	Not known	Asthenia, weight loss
Investigations	Not known	Electrocardiogram QT prolonged (see section 4.4 and 4.5) Blood glucose increased (see section 4.4) Blood uric acid increased (see section 4.4) 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; website: 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 2.5 mg per day 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 effect is of mild intensity. At this antihypertensive dose of 2.5 mg per day, indapamide 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 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:

- 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 in diabetic hypertensive subjects.

Lastly, the co-prescription of indapamide 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 after oral administration. Peak blood levels are obtained after 1 or 2 hours.

Distribution

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.

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

Lactose

Maize starch
Polyvidone
Magnesium stearate

Seal coat:
Opaseal (polyvinylacetate phthalate, ethyl acetate and stearic acid)
Purified talc

Subcoat:

Calcium carbonate
Acacia
Titanium dioxide (E171)
Purified talc
Sucrose

Smoothing Syrup:
Sucrose

Colour Coat:

Sucrose
Titanium dioxide (E171)

Smoothing Syrup:
Sucrose

Polishing Coat:
Opaglos 6000P (shellac, carnauba wax yellow and beeswax white)

6.2 Incompatibilities

None known

6.3 Shelf life

Blister Packs - 4 years

Polypropylene tablet containers – 3 years

6.4 Special precautions for storage

Tablet containers: Do not store above 25°C. Keep the container tightly closed.

Blisters: Do not store above 25ºC. Store in the original package

6.5 Nature and contents of container

1. Polypropylene tablet containers 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

None

7 MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd

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Watford

Hertfordshire

WD18 9SS

Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0118

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27/3/2006

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04/04/2018