1. NAME OF THE MEDICINAL PRODUCT

Indapamide Hemihydrate 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg indapamide hemihydrate.

Excipient with known effect:
Each tablet contains 50 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Indapamide tablets are 6.5 mm white biconvex film coated tablet, marked “IE 2.5” on one side and “G” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indapamide hemihydrate tablets are indicated for the oral treatment of essential hypertension.

Indapamide hemihydrate tablets may be used as sole therapy or combined with other antihypertensive agents.

4.2 Posology and method of administration

Posology

Adults
The dosage is one tablet, containing 2.5 mg indapamide hemihydrate, daily to be taken in the morning.

Patients with renal failure (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.

Older people (see section 4.4)
In the older people, the plasma creatinine must be adjusted in relation to age, weight and gender. Older people can be treated with indapamide when renal function is normal or only minimally impaired.

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

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

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 2.5 mg indapamide daily is not recommended as there is no appreciable additional antihypertensive 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 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. The co-administration of indapamide with diuretics may cause hypokalaemia and, therefore, is not recommended.

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

Method of administration
Indapamide tablets are for oral administration only.

4.3 Contraindications

Hypersensitivity to the active substance, to other sulfonamides or to any of the excipients listed in section 6.1.

Severe renal failure

Hepatic encephalopathy, severe impairment of liver function, severe hepatic failure

Hypokalaemia

Recent cerebrovascular accident.

4.4 Special warnings and precautions for use

In case of hepatic impairment, thiazide-related diuretics may cause hepatic **encephalopathy, particularly in case of electrolyte imbalance. 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.

Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that photosensitivity leading to exaggerated sunburn may occur and treatment should be discontinued at the first sign of skin erythema.

Angioneurotic oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported infrequently in patients receiving treatment with indapamide. In such cases, treatment with indapamide should be stopped immediately and the patient should be monitored until the oedema has disappeared.

Water and electrolyte balance

Plasma sodium
Plasma sodium must be measured before treatment is initiated and subsequently at regular intervals. Any kind of treatment with diuretics may cause hyponatraemia, sometimes with very serious consequences. A drop in plasma sodium may be asymptomatic in the beginning. Therefore, regular monitoring is essential and should be carried out even more frequently in elderly patients and in

cirrhotic patients (see sections 4.8 and 4.9). 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 constitutes the greatest risk in the treatment with thiazides and related diuretics. 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 (see section 4.5), cirrhotic patients with oedema and ascites, coronary artery disease, cardiac failure patients, patients with hyperaldosteronism, patients predisposed to or suffering from gout.

In cardiac patients, hypokalaemia increases the cardiac toxicity of digitalis preparations (e.g. digoxin) 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 and subsequently at regular intervals, especially in the mentioned risk patients.

If hypokalaemia (< 3.4 mmol potassium) is detected, it must be corrected and it should be prevented in risk patients. 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
Thiazides and related diuretics may decrease urinary calcium excretion and cause a slight and transitory increase in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment with indapamide hemihydrate should be stopped if hypercalcaemia occurs in patients with hyperparathyroidism.

Treatment should be withdrawn before the investigation of parathyroid function.

Blood glucose
Monitoring of blood glucose is important in diabetic patients, especially in the presence of hypokalaemia.

Uric acid
Serum urate should be monitored in patients with gout. Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics
Caution should be exercised when administering indapamide hemihydrate to patients with severe renal impairment. However, the drug has been safely given to patients with impaired renal function. However, if renal insufficiency worsens, treatment should be stopped.

Thiazides and related diuretics are fully effective at normal or only minimally impaired renal function (plasma creatinine below levels of the order of 25 mg/l, i.e. < 220 µmol/l in an adult). In elderly patients, the plasma creatinine values must be adjusted according to age, body weight and sex.

Secondary hypovolaemia, as a result of loss of water and sodium induced by the diuretic at the start of treatment results in reduced glomerular filtration which, may increase plasma concentrations of blood urea and creatinine. This temporary impairment of renal function is harmless to patients with normal renal function but may exacerbate pre-existing renal insufficiency.

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. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. 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.

Athletes
The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, which may give a positive result in doping tests.

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

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

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol, haloperidol)

- others: bepridil, cisapride, diphemanil, 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.

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 (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 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 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 predisponse to the toxic effects of digitalis.
Monitoring of plasma potassium, magnesium and ECG and, if necessary, adjust the treatment.

<u>Combinations to be taken into consideration</u>

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 ciclosporin 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
There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide 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 hemihydrate 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.

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 frequencies:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	**Adverse Event**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia	Very rare
Metabolism and nutrition disorders	Hypokalaemia (see section 4.4)	Common
	Hyponatraemia (see section 4.4)	Uncommon
	Hypochloraemia, hypomagnesaemia,	Rare
	Hypercalcaemia	Very rare
	Loss of weight	Not known
Nervous system disorders	Fatigue, headache, paraesthesia, vertigo	Rare
	Dizziness, syncope	Not known
Eye disorders	Myopia, blurred vision, choroidal effusion, visual impairment	Not known
Cardiac disorders	Arrhythmia	Very rare
	Torsades de pointes (potentially fatal) (see sections 4.4 and 4.5)	Not known
Vascular disorders	Orthostatic hypotension	Uncommon
	Hypotension	Very rare
Gastrointestinal disorders	Vomiting	Uncommon
	Nausea, constipation, dryness of the mouth	Rare
	Pancreatitis	Very rare
Hepatobiliary disorders	Abnormal hepatic function	Very rare
	Possibility of onset of hepatic encephalopathy in patients with impaired liver function (see sections 4.3 and 4.4), hepatitis	Not known

System Organ Class	Adverse Event	Frequency
Skin and subcutaneous tissue disorders	Hypersensitivity reactions, mainly dermatological, may be observed in patients predisposed to allergic and asthmatic manifestations: Maculopapular rash	Common
	Purpura	Uncommon
	Erythema multiforme	Rare
	Angioneurotic oedema, urticaria, toxic epidermal necrolysis, Steven Johnson syndrome	Very rare
	Photosensitivity (see section 4.4), possible exacerbation of acute disseminated lupus erythematosus	Not known
Musculoskeletal and connective tissue disorders	Muscular cramps	Rare
Renal and urinary disorders	Renal failure	Very rare
	Renal insufficiency	Not known
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
	Impotence	Not known
Investigations	Electrocardiogram QT prolonged (see sections 4.4 and 4.5), elevated liver enzyme levels, increased blood uric acid (see section 4.4), hyperglycaemia (see section 4.4)	Not known

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.

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.

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

Indapamide is a non-thiazide sulfonamide with an indole ring, belonging to the diuretic family which has certain structural similarities to furosemide as well as the thiazides and has actions and uses similar to those of chlorothiazide.

Diuresis is initiated within about 1 to 2 hours and has been reported to last for up to 36 hours. Its inhibitory action on carbonic anhydrase is only weak. At the dose of 2.5 mg per day indapamide exerts a prolonged antihypertensive activity in hypertensive human subjects.

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 sub-clinical.

Mechanism of action
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 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 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 (beta-blockers, 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 gastrointestinal tract and peak plasma concentrations are seen 1-2 hours after oral dosing.

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.
Biotransformation and elimination
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 core
Lactose
Cellulose, microcrystalline
Sodium starch glycolate
Croscarmellose Sodium Type A
Magnesium stearate

Tablet film coat
Hypromellose
Macrogol 400

Titanium dioxide (E171)

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool dry place.

Use as directed by a physician

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Securitainers with urea white caps and “Jayfilla” ullage filler, containing 30, 60, 100, 250 or 500 tablets.

Blister packs containing 28, 30, 56 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Generics (U.K.) Limited T/A Viatris,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 04569/0232

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 July 1991

Date of latest renewal: 11 October 1996

10 DATE OF REVISION OF THE TEXT

13/04/2026