SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide 2.5mg coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Indapamide as Indapamide hemihydrate 2.5 mg.
For excipients, see 6.1

3 PHARMACEUTICAL FORM

White, circular, sugar coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration:

Adults:

The dosage is one tablet, containing 2.5mg Indapamide, to be taken daily in the morning

The action of Indapamide is progressive and the reduction in blood pressure may continue and not reach a maximum until several months after the start of therapy.

A larger dose than 2.5mg of Indapamide daily is not recommended as there is no appreciable additional anti-hypertensive effect but a diuretic effect may become apparent. If a single daily tablet of Indapamide does not achieve a sufficient reduction in blood pressure, another anti-hypertensive agent may be added such as beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents.

The co-administration of Indapamide with diuretics which may cause hypokalaemia is not recommended. (see section 4.5)

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

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.

Elderly (see sections 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 and 4.4)

In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:

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

Administration:

Route of administration: Oral.

4.3 Contraindications

Hypersensitivity to indapamide, to other sulphonamides or to any of the excipients.

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 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 fructose intolerance, glucosegalactose malabsorption of 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 section 4.8 and 4.9). Any diuretics 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 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 (affect the parathyroid gland above the kidney).

  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. Use with caution in patients with nephrotic syndrome

- **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.
  - Indapamide may cause exacerbation of systemic lupus erythematosus.

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

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations:

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 are required.

Combinations requiring precautions for use:

Torsades de pointes-inducing drugs:

- Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide, flecainide)

- Class III antiarrhythmics (amiodarone, bretylium, sotalol, dofetilide, ibutilide),

- Some antipsychotics :

    - Phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine)

    - Benzamides (amisulpride,sulpiride, sultropride tiapride)

    - Butyrophenones (droperidol, haloperidol)

- Others: atomoxetine, astemizol, 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.

N.S.A.I.Ds. (systemic route), including COX-2 selective inhibitors, high dose salicylic acid (≥3g/day):
Possible decrease in 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 a converting enzyme inhibitor is started in the presence of pre-existing sodium depletion (in particular in individuals 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 only gradually.

In congestive cardiac failure, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the combined 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 mineralocorticoids (systemic), tetracosactide, stimulant laxatives, reboxetine, beta-2 sympathomimetics, 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. Monitor plasma potassium, ECG and adjust treatment if necessary.

Combinations which must 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.

Monitor plasma potassium, ECG if required and adjust treatment if necessary.

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/litre (135µmol/litre) in men and 12mg/litre (110µmol/litre) 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.

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-adrenoreceptor 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 alphablockers 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, resulting from decreased urinary calcium elimination.

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):
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 sulfonamidederived 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 (dizziness) 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. Occurrence of dizziness may interfere with driving.
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 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 effects 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, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Body System	**Frequency**	**Adverse Event**
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Metabolism and nutrition	Very rare	Hypercalcaemia disorders
	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, choroidal effusion
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	Uncommon	Vomiting

disorders		
	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 section4.4) 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 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

Indapamide has been found free of toxicity at up to 40 mg, *i.e.* 16 times the therapeutic dose.

Expected symptoms of overdosage would be electrolyte imbalance (hyponatraemia, hypokalaemia), hypotension, nausea, vomiting, vertigo, drowsiness, confusion, muscular weakness, gastro intestinal disturbances, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

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: C03 BA11

Indapamide is an indoline derivative of chlorsulphonamide which shares many chemical, pharmacodynamic and therapeutic similarities with other sulphonamide diuretics. In addition to its diuretic activity indapamide has been shown to decrease vascular smooth muscle reactivity and peripheral resistance in various in-vitro and in-vivo models.

The antihypertensive effect is also due to the stimulation of the synthesis of prostanglandin PGE_2 and the vasodilator and platelet antiaggregant prostacyclin PGI_2. In addition, the vasodilator action of bradykinin has contributing effect to the over-all vascular mechanism of action of indapamide.

The combined prescription of indapamide with other anti-hypertensives (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

General Characteristics of the active substance-

Indapamide is rapidly and completely absorbed from the gastro-intestinal tract and peak plasma concentrations are seen 1-2 hours after oral dosing.

Indapamide is rapidly absorbed from the gastrointestinal tract. Elimination is biphasic with a terminal half-life of 14 to 18 hours. It is extensively metabolised. About 60 to 70% of the dose has been reported to be excreted in the urine; only about 5% is excreted unchanged. Indapamide is about 71 to 79% bound to plasma proteins and it is preferentially taken up in the red blood cells.

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
Povidone
Magnesium Stearate (E572)
Calcium Carbonate
Titanium Dioxide (E171)
Purified Talc
Sucrose
Acacia

Opaseal (composition- Industrial methylated spirits, Polyvinyl Acetate Phthalate, Purified water, Ethyl Acetate, Stearic Acid (E570)
Opaglos 6000P (Composition- Industrial methylated spirits, Yellow Carnauba Wax (E903)
Bees Wax (E901) and Shellac (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

a. Do not store above 25°C.
b. Keep the container tightly closed (plastic bottles)
c. Store in the original package (for blister packs)

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, 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

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pharmvit Limited
177 Bilton Road
Perivale
Greenford
Middlesex UB6 7HQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04556/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2003
Date of latest renewal: 02 Sept 2008

10 DATE OF REVISION OF THE TEXT

22/06/2020