

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indapamide 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indapamide 2.5mg

For excipients see 4.4 and 6.1

3 PHARMACEUTICAL FORM

Coated tablet

White, biconvex, sugar coated tablet printed with the company logo or printed with "T"

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of essential hypertension

4.2 Posology and method of administration

Oral use

Adults:

The dosage of one tablet, containing 2.5mg indapamide, to be taken daily in the morning. The action of indapamide is progressive and the reduction in blood pressure may continue and not reach a maximum until several months after the start of therapy. A larger dose than 2.5mg of indapamide daily is not recommended as there is no appreciable additional anti-hypertensive effect but a diuretic effect may become apparent. If a single daily tablet of indapamide does not achieve a sufficient reduction in blood pressure, another anti-hypertensive agent may be added such as beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents.

The co-administration of indapamide with diuretics that may cause hypokalaemia is not recommended.

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 30ml/min), treatment is contraindicated.

Thiazides and related diuretics are fully effective only when renal function is

normal or only minimally impaired.

Elderly (see section 4.4):

In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with indapamide when renal function is normal or only minimally impaired.

Hepatic impairment (see sections 4.3 and 4.4)

In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:

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

4.3 Contraindications

Severe renal failure

Hepatic encephalopathy or severe impairment of liver function

Hypokalaemia

Hypersensitivity to sulfonamides, indapamide or any other ingredients

Porphyria

Addison's disease

Refractory hypokalaemia, hyponatraemia, hypercalcaemia

4.4 Special warnings and precautions for use

Warnings:

When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy. 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 have been reported with thiazide and thiazide-related diuretics (see section 4.80). If a photosensitivity reaction occurs during treatment, it is recommended to stop indapamide. If re-administration of indapamide is considered necessary, it is recommended to protect exposed areas from the sun or artificial UVA.

Precautions:

- Water and electrolyte balance:

Plasma sodium:

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretics treatment may cause hyponatraemia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (See Adverse reactions and Overdose sections).

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, ie the elderly, malnourished and/or poly-medicated, patients with hyperaldosteronism, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients.

In this latter situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias. Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a pre-disposing factor to the onset of severe arrhythmias, in particular, potentially fatal torsades de pointes.

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

Plasma calcium:

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

Treatment should be withdrawn before the investigation of parathyroid function.

- Blood glucose:

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

- Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

- Renal function and diuretics:

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

- There is no evidence of rebound hypertension on withdrawal of indapamide.
- Indapamide may cause exacerbation of systemic lupus erythematosus.
- Patients with rare hereditary problems of fructose or galactose intolerance, the LAPP lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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.

Long term treatment with this type of diuretic may reduce excretion of lithium.

Combinations requiring precautions for use:

Torsade de pointes-inducing drugs:

Hypokalaemia caused by indapamide increases the risk of ventricular arrhythmias, particularly torsade de pointes, when indapamide is used in combination with medications which prolong the QT interval or induce torsade de pointes. Hypokalaemia should be corrected before introducing any of the following medications. Monitoring of plasma electrolytes, ECG and clinical symptoms is required during concurrent use. Where possible, alternative

substances which do not cause torsade de pointes in the presence of hypokalaemia should be used.

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide, flecainide)
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics: phenothiazines (chlorpromazine, cyamemazine, levopromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol),
- Others: pimozone, sertindole, zotepine,
- atomoxetine
- macrolide antibiotics (erythromycin especially by IV route, clarithromycin)
- quinolone antibiotics (moxifloxacin)
- antihistamines (astemizole, mizolastine)
- pentamidine
- bepridil
- cisapride
- diphemanil
- halofantrine
- sparfloxacin
- vincamine IV

Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

Digitalis preparations:

Hypokalaemia may potentiate the action of digoxin, and increase the toxic effects of digoxin and other cardiac glycosides.

Monitor plasma potassium, ECG and adjust treatment if necessary.

NSAIDs (systemic), high dose salicylates:

Possible decrease in antihypertensive effect of indapamide.

Acute renal failure in dehydrated patients (decreased glomerular filtration).

Hydrate the patient; monitor renal function at the start of treatment.

Other compounds causing hypokalaemia:

There is increased risk of hypokalaemia when indapamide is used in

combination with other medications which cause hypokalaemia (additive effect). Plasma potassium levels should be monitored and corrective action taken if necessary.

- amphotericin B (IV)
- glucocorticoids (systemic), mineralocorticoids (systemic), tetracosactide
- stimulant laxatives
- reboxetine
- beta-2 sympathomimetics
- theophylline
- diuretics

The co-administration of indapamide with diuretics which may cause hypokalaemia (e.g. bumetanide, furosemide, thiazides, xipamide) is not recommended. At doses higher than that recommended for hypertension, indapamide has a diuretic effect.

Angiotensin converting enzyme (ACE) inhibitors:

There is a risk of sudden hypotension and/or acute renal failure when treatment with an ACE 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 ACE inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the ACE inhibitor and increase only gradually. In congestive cardiac 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.

Angiotensin-II receptor agonists

See ACE-inhibitors.

Baclofen:

Increased antihypertensive effect.

Hydrate the patient; monitor renal function at the start of treatment.

Anti-arrhythmic agents

(see also *Torsade de pointes-inducing drugs*)

Hypokalaemia antagonises the effects of lidocaine and mexiletine and increases cardiac toxicity with flecainide.

Combinations which must be taken into consideration:*Potassium-sparing diuretics (amiloride, spironolactone, triamterene):*

Such rational combinations, useful in certain patients, do not eliminate the possibility of hypokalaemia or, in particular in renal failure and diabetic patients, of hyperkalaemia.

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

Metformin:

In the presence of functional renal insufficiency related to diuretics and more particularly to loop diuretics, increased risk of metformin induced lactic acidosis. 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.

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, methyl dopa, 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.

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 Pregnancy and lactation

Pregnancy

As a general rule, the administration of diuretics should be avoided in pregnant women and should never be used to treat physiological oedema of pregnancy. Diuretics can cause foetoplacental ischaemia, with a risk of impaired foetal growth.

Breast feeding

Breast feeding is inadvisable, because indapamide is excreted in human milk.

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

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

Thiazide-related diuretics, including indapamide, may cause:

Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common, $\geq 1/10$; common, $\geq 1/100$ and $< 1/10$; uncommon, $\geq 1/1000$ and $< 1/100$; rare, $\geq 1/10000$ and $< 1/1000$; very rare, $< 1/10000$ and frequency not known (not known from the data available).

An asterisk (*) indicates that additional information on the respective undesirable effect is provided below the table.

Body System	Frequency	Adverse Event
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders	Unknown	Hypersensitivity reactions *
Metabolism and nutrition disorders		
	Very rare	Hypercalcaemia

	Unknown	Potassium depletion with hypokalaemia, particularly in certain high risk populations (see section 4.4) Hyponatraemia * with hypovolaemia responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight. Hyperuricaemia * Hyperglycaemia *
Nervous system disorders	Rare	vertigo, fatigue, headache, paraesthesia
	Not known	Syncope
Eye disorders	Unknown	Visual disturbances
Cardiac disorders	Very rare	Palpitations, cardiac arrhythmias (see section 4.4)
	Not known	Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)
Vascular disorders	Very rare	Orthostatic hypotension
Gastrointestinal disorders	Uncommon	Vomiting
	Rare	Nausea, constipation, dry mouth
	Very rare	Pancreatitis
Hepatobiliary disorders	Very rare	Abnormal hepatic function
	Not known	Hepatic encephalopathy * Hepatitis
Skin and subcutaneous tissue disorders	Common	Maculopapular rashes
	Uncommon	Purpura
	Very rare	Angioneurotic oedema, urticaria, Erythema multiforme, toxic epidermal necrolysis, Stevens Johnson Syndrome
	Frequency not known	Worsening of pre-existing acute disseminated lupus erythematosus Photosensitivity reactions (see section 4.4) Pruritus

Musculoskeletal and connective tissue disorders	Frequency unknown	Muscle cramps, possible worsening of pre-existing acute disseminated lupus erythematosus
Renal and urinary disorders	Very rare	Renal failure *
Reproductive system and breast disorders	Frequency unknown	Impotence
General disorders	Frequency unknown	asthenia, weight loss
Investigations	Not known	Electrocardiogram QT prolonged Blood glucose increased and blood uric acid increased during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes Elevated liver enzyme levels

Additional information

**Hypersensitivity reactions.* Hypersensitivity reactions may occur especially in individuals with a history of allergy or asthma.

**Hypokalaemia.* During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/L) was seen in 10% of patients and <3.2 mmol/L in 4% of patients after four to six weeks of treatment. After twelve weeks treatment, the mean fall in plasma potassium was 0.23 mmol/L.

Hypokalaemia may be particularly serious in high-risk populations (see section 4.4).

**Hyponatraemia.* Hyponatraemia with dehydration and hypovolaemia may occur. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis.

Warning signs of electrolyte disturbances include increased thirst, confusion, muscle cramps, muscle weakness and disorders of cardiac rhythm.

**Hyperuricaemia.* Increase serum uric acid levels and may precipitate attacks of gout in some patients.

**Hyperglycaemia.* Indapamide may provoke increases in blood sugar levels and glycosuria. In patients with diabetes mellitus, this may lead to a slight reduction in glucose tolerance and deterioration of diabetes control.

**Hepatic encephalopathy.* Hepatic encephalopathy may occur in patients with hepatic insufficiency (see sections 4.3 and 4.4).

**Renal failure.* Abnormal renal function test values (increased blood urea, increased creatinine) have been reported in association with hypovolaemia.

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

4.9 Overdose

Expected symptoms of overdosage would be electrolyte imbalance, hypotension, gastrointestinal disturbances and muscular weakness. Treatment would be symptomatic, directed at correcting the electrolyte abnormalities and emesis or gastric lavage should be considered.

Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

C03B A11 – Low-ceiling diuretics, excl. thiazides, sulfonamides, plain

Indapamide is an indoline derivative of chlorsulfonamide which shares many chemical, pharmacodynamic and therapeutic similarities with other sulfonamide 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.

5.2 Pharmacokinetic properties

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. About 16-23% of administered dose is excreted in the faeces. 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.

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 25°C. 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 Shasun (UK) Ltd

Unit 4 Metro Centre

Tolpits Lane

Watford

Hertfordshire

WD18 9SS

Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0118

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/3/2006

10 DATE OF REVISION OF THE TEXT

20.05.2016

11 DOSIMETRY (IF APPLICABLE)

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable