SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> <STRENGTH> Tablets

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains <STRENGTH> of indapamide hemihydrate.

Excipient with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Tablet

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Indapamide is indicated in the treatment of essential hypertension. Indapamide may be used as sole therapy or combined with other antihypertensive agents.

* 1. Posology and method of administration

**Posology**

**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 of blood pressure may continue and not reach a maximum until several months after the start of therapy. A larger dose than 2.5mg 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.

There is no evidence of rebound hypertension on withdrawal of indapamide

*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 SR when renal function is normal or only minimally impaired.

**Paediatric populations:**

The safety and efficacy of indapamide 2.5mg in children and adolescents have not been established. No data are available.

**Method of administration**

Oral use.

* 1. Contraindications

Severe renal failure.

Hepatic encephalopathy or severe impairment of liver function.

Hypokalaemia.

Hypersensitivity to Indapamide, Sulphonamide derivatives, and any of the ingredients.

* 1. 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 diureticmust be stopped immediately if this occurs or there are signs of renal insufficiency.

A slight weight loss has been reported in some patients taking Indapamide.

*Excipients (Lactose Monohydrate and Sucrose):*

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

*Photosensitivity:*

Cases of photosensitivity reactions have been reported with thiazides and thiazide-relateddiuretics (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.’

*Special precautions for use:*

* **Water and electrolyte balance:**
* *Plasma Sodium:*

This must be measured before starting treatment, then at regular intervals subsequently. Anydiuretics 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 sections4.8 and 4.9).

* *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 theorigin 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 depointes.

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement should be obtained during the first week following the start oftreatment.

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 andtransitory rise in plasma calcium. Hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment should be withdrawn before the investigation of parathyroid function. Indapamidemay reduce the level of PTH.

* + **Blood Glucose:**

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

* + **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. 220[μmol/lin an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.

Hypovalaemia, 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 bloodurea 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.

* + **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 acuteangle-closure glaucoma may include a history of sulfonamide or penicillin allergy

* + **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..

* 1. Interaction with other medicinal products and other forms of interaction

Combinations that are not recommended:

**Lithium:**

Increased plasma Lithium with signs of overdose, as with a salt-free diet (decreased urinaryLithium secretion). 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 antiarrhythmic drugs (Quinidine, Hydroquinidine, Disopyramide), Class III antiarrhythmics (Amiodarone, Bretylium, Sotalol dofetilide, ibutilide)

**Some antipsychotics:**

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

others: bepridil, cisapride, diphemanil, mizolastine, sparfloxacin, moxifloxacin, IV-erythromycin, Halofantrine, Pentamidine, SultoprideTerfenadine, Vincamine IV.

Increased risk of ventricular arrhythmias, particularly Torsade de pointes (hypokalaemia is arisk 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 torsade de pointes in thepresence of hypokalaemia.

**N.S.A.I.Ds. (systemic route) including COX-2 selective inhibitors, high dose salicylicacid (≥ 3 g/day):**

Possible decrease in anti-hypertensive effect of Indapamide.

Risk of acute renal failure in dehydrated patients (decreased glomerular filtration). Hydratethe 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.Einhibitor 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 isnecessary:

* 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 cardiac failure, start with a very low dose of A.C.E inhibitor, possibly after areduction in the dose of the combined hypokalaemic diuretic.

In all cases, monitor renal function (plasma creatinine) during the first weeks of treatmentwith an A.C.E inhibitor.

**Other compounds causing hypokalaemia: amphotericin B (IV), gluco-andmineralocorticoids (systemic route), tetracosactide, stimulant laxatives**

Increased risk of hypokalaemia (additive effect).

Monitoring of plasma potassium and correction if required. Must be particularly borne inmind in case of concomitant digitalis treatment.Use non-stimulant laxatives.

**Baclofen:**

Increased anti-hypertensive 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 hypersensitivityreactions to allopurinol.

*Combinations to 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 andECG should be monitored and, if necessary, treatment reviewed.

**Metformin**

Increased risk of metformin induced lactic acidosis due to the possibility of functional renalfailure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds15mg / 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, inparticular when large doses of iodinated contrast media are used. Rehydration before administration of the iodinated compound.

**Imipramine-like Antidepressants (Tricyclics), Neuroleptics:**

Anti-hypertensive effect and risk of orthostatic hypotensive increased (additive effect).

**Calcium salts:**

Risk of hypercalcaemia resulting from decreased urinary calcium elimination.

**Ciclosporin / Tacrolimus:**

Risk of increased plasma creatinine without any change in, circulating cyclosporine/tacrolimus levels, even in the absence of water / sodium depletion.

**Corticosteroids, tetracosactide (systemic route):**

Decreased anti-hypertensive effect (water / sodium retention due to corticosteroids).

* 1. 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.

* 1. 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.

* 1. 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 andmaculopapular rashes.

Tabulated summary of adverse reactions

The following undesirable effects have been observed with indapamide during treatmentranked under the following frequency:

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 (≥1/100,000 to <1/10,000), not known (cannot be estimated from the available data).

| **MeDRA System Organ Class** | **Undesirable Effects** | **Frequency** |
| --- | --- | --- |
| Blood and the lymphatic System Disorders | Agranulocytosis | Very rare |
| Aplastic anaemia | Very rare |
| Haemolytic anaemia | Very rare |
| Leucopenia | Very rare |
| Thrombocytopenia | Very rare |
| Metabolism and Nutrition Disorders | Hypercalcaemia | Very rare |
| Hypokalaemia (see section 4.4) | Common |
| Hyponatraemia (see section 4.4) | Uncommon |
| Hypochloraemia | Rare |
| Hypomagnesaemia | Rare |
| Reproductive System and breast disorders | Erectile dysfunction | Uncommon |
| Nervous System disorders | Vertigo | Rare |
| Fatigue | Rare |
| Headache | Rare |
| Paraesthesia | Rare |
| Syncope | Not known |
| Eye disorders | Myopia | Not known |
| Blurred vision | Not known |
| Visual impairment | Not known |
| Choroidal effusion | Not known |
| Cardiac Disorders | Arrhythmia | Very rare |
| Torsade de pointes (potentially fatal) (seesections 4.4 and 4.5) | Not known |
| Vascular Disorders | Hypotension | Very rare |
| Gastrointestinal Disorders | Vomiting | Uncommon |
| Nausea | Rare |
| Constipation Rare | Rare |
| Dry mouth | Rare |
| Pancreatitis | Very rare |
| Hepatobiliary Disorders | Abnormal hepatic function | Very rare |
| Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4) | Not known |
| Hepatitis | Not known |
| Skin and Subcutaneous Tissue Disorder | Hypersensitivity reactions | Common |
| Maculopapular rashes | Common |
| Purpura | Uncommon |
| Angioedema | Very rare |
| Urticaria | Very rare |
| Toxic epidermal necrolysis | Very rare |
| Stevens-Johnson Syndrome | Very rare |
| Possible worsening of pre-existing acutedisseminated lupus erythematosus | Not known |
| Photosensitivity reactions (see section 4.4) | Not known |
| Renal and Urinary Disorders | Renal failure | Very rare |
| Investigations | Electrocardiogram QT prolonged (seesections 4.4 and 4.5) | Not known |
| Blood glucose increased (see section 4.4) | Not known |
| Blood uric acid increased (see section 4.4) | Not known |
| Elevated liver enzyme levels | Not known |

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:

* 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 Health Product Vigilance Center; HPVC

* 1. Overdose

**Symptoms:**

Indapamide has been found free of toxicity at up to 40mg, 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.

1. PHARMACOLOGICAL PROPERTIES
   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. At the dose of 2.5mg per day indapamide exerts a prolonged antihypertensive activity in hypertensive human subjects.

Dose-effect studies have demonstrated that, at the dose of 2.5mg per day, the antihypertensive effect is maximal and the diuretic effect is sub-clinical.

At this antihypertensive dose of 2.5mg 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.

* 1. Pharmacokinetic properties

Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are obtained after 1 to 2 hours.

Elimination is biphasic with a terminal half-life of 14 to 18 hours only about 5% is excreted unchanged. It is extensively metabolised. About 60% to be excreted in the urine. About 70% of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is about 71 to 79% bound to plasma proteins and it is preferentially taken up in the red blood cells. It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility.

Indapamide is metabolised to a marked degree with 7% of the unchanged product found in the urine during the 48 hours following administration.

* 1. 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.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

Not applicable.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>