Summary of Product Characteristics Induric SR Tablets (Indapamide Sustained Release Tablets 1.5mg)

1. **Name of the Medicinal Product**
   Induric SR Tablets 1.5 mg

2. **Qualitative and Quantitative Composition**
   Each sustained release tablet contains Indapamide hemihydrate equivalent 1.5 mg of Indapamide.

3. **Pharmaceutical Form**
   Sustained Release Tablet

4. **Clinical Particulars**

4.1 Therapeutic Indications

Essential hypertension.

4.2 Posology and Method of administration

For oral administration.

One tablet per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed. At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

Renal failure:
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:
In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with Induric 1.5 mg slow-release Tablets when renal function is normal or only minimally impaired.

Patients with hepatic impairment:
In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:
Induric 1.5 mg slow-release Tablets are not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to indapamide, other sulphonamides or any ingredients in the tablets.
- Severe renal failure.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.

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.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment.

Special precautions for use
Water and electrolyte balance:

Plasma sodium:
This must be measured before starting treatment, then at regular intervals subsequently.

Plasma potassium:
Potassium depletion with hypokalaemia is the major risk of thiazide 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, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients

Plasma calcium:
Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. 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/l, i.e. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions may occur with lithium, digoxin, alcohol, narcotics and barbiturates.
No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants, uricosurics and anti-inflammatory agents.
It is recommended that the drug not be used in combination with a diuretic agent since the combination may produce hypokalaemia and hyperuricaemia.
When Indapamide is given with other nondiuretic antihypertensive agents, the effects on blood pressure are additive.

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.

Lactation
Indapamide is excreted in human milk. Effects on the breast-fed child are likely and therefore indapamide is not recommended during breast-feeding.

4.7 Effects on ability to drive and use machines

Indapamide has a minor or moderate influence on the ability to drive and use machines. Indapamide does not affect vigilance. However, in individual cases the hypotensive effect may impact on a patient's ability to drive and operate machinery, especially at the start of treatment or when another antihypertensive agent is added.

4.8 Undesirable effects

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).

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 (A.C.E.) inhibitors:

Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. 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 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 heart failure, start with a very low dose of A.C.E. 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 A.C.E. 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 predisposing to the toxic effects of digitalis.
Monitoring of plasma potassium and ECG and, if necessary, adjust the treatment.

5 Overdose

Symptoms:

Indapamide has been found free of toxicity at up to 40 mg, i. e. 27 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).

Treatment:

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.

6 Pharmacological Properties

6.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antihypertensive diuretics, Sulfonamides, plain
ATC code: C03BA11
Indapamide is a sulphonamide derivate with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the

urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.
Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.
The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.

Indapamide reduces left ventricular hypertrophy.
Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.
It has also been shown, in the short-, mild- and long-term in hypertensive patients, that indapamide:

- Does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL- cholesterol;
- Does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

6.2 Pharmacokinetic Properties

Absorption
The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract. Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed. Peak serum level following a single dose occurs about 12 hours after ingestion; repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

Distribution
Binding of indapamide to plasma proteins is 79%. The plasma elimination half-life is 14 to 24 hours (mean 18 hours). Steady state is achieved after 7 days. Repeated administration does not lead to accumulation.

Metabolism
Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites.

High risk individuals
Pharmacokinetic parameters are unchanged in renal failure patients.

6.3 Preclinical safety data

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. Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

7 Pharmaceutical Particulars

7.1 List of Excipients

Methocel K15 CR,
Microcrystalline Cellulose BP
Colloidal Anhydrous Silica BP
Magnesium Stearate BP

7.2 Incompatibilities

Not applicable

7.3 Shelf life

2 Years

7.4 Special precautions for storage

Store in a dry place below 30 °C. Protect from light

7.5 Nature and contents of container

ALU/ALU blister packing

7.6 Instructions for use, handling and disposal

No special requirements

8 Registrant

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9 Manufacturer

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11 Dosimetry (if applicable)
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12 Instructions for Preparation of radiopharmaceuticals (if applicable)
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