Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Icorvida SR 1.5mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 1.5 mg indapamide.

Excipient with known effect
Each prolonged-release tablet contains 97.58 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet
White, round, slightly biconvex film coated-tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Icorvida SR is indicated in essential hypertension in adults.

4.2 Posology and method of administration

Posology

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

Special populations

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

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.

Paediatric population
The safety and efficacy of Icorvida SR in children and adolescents have not been established. No data are available.

Method of administration
Indapamide is administered orally.

4.3 Contraindications

Indapamide is contraindicated in:

- hypersensitivityto the active substance, to other sulfonamides or to any of the excipients listed in section 6.1;

- severe renal failure;
- hepatic encephalopathy or severe impairment of liver function;
- hypokalaemia.

4.4 Special warnings and precautions for use

Special warnings

In patients with impaired liver function, thiazide-related diuretics may cause hepatic encephalopathy which can progress to hepatic coma, 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 indapamide 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. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential. In the elderly and cirrhotic patients, monitoring should be even more frequent (see sections 4.8 and 4.9). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible of 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

The major risk of treatment with thiazide and related diuretics is hypokalaemia. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk groups, i.e. patients that are malnourished and/or are taking several drugs concomitantly, the elderly, cirrhotic patients with oedema and ascites, patients with coronary artery disease and cardiac failure. In these patients, hypokalaemia increases the cardiotoxicity of digitalis preparations and the risks of arrhythmias.

Patients 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 heart rhythm disorders of the type "torsades de pointes".

In these patients, more frequent monitoring of plasma potassium is required. The first measurement of plasma potassium should be obtained during the first week of treatment.

If low potassium levels are detected, correction is required. 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 and transitory rise in plasma calcium. Evident hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment with the diuretic 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 levels below 25 mg/l, i.e. 220 µmol/l in adults). 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 transient renal dysfunction has no consequences in patients with normal renal function but it may deteriorate the existing renal insufficiency.

Athletes
The attention of athletes is drawn to the fact that this product contains an active substance which may cause a positive reaction in doping tests.

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

Lactose
This medicinal product contains 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
Concomitant use of lithium may lead to increase of plasma lithium concentration with signs of overdosage, as with a sodium-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment is required.

Combinations requiring precaution for use
Torsades de pointes-inducing drugs

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide, bretylium),
- some antipsychotics:
- phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
- benzamides (amisulpride, sulpiride, sultopride, tiapride),
- butyrophenones (droperidol, haloperidol),
- other antipsychotic (e.g pimozide),
- other substances (e.g.: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV, methadone, astemizole, terfenadine).

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.

Non-steroidal anti-inflammatory drugs (systemic route) including COX-2 selective inhibitors, high dose acetylsalicylic 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
When treatment with an ACE inhibitor is initiated, sudden hypotension and/or acute renal failure may occur in patients with pre-existing depletion of sodium (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 non-potassium-sparing 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), tetracosactide, stimulant laxatives

The risk of hypokalaemia is increased (additive effect).

Plasma potassium should be monitored and corrected if necessary. Caution is required in patients concomitantly taking digitalis. These patients should take non-stimulant laxatives.

Baclofen
Increased antihypertensive effect.
The patient should drink sufficient quantity of liquid; renal function is monitored 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 hypersensitivity reactions 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 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 patients dehydrated due to diuretics, the risk of acute renal failure is increased, particularly when large doses of iodinated contrast media are used. The patient should be rehydrated prior to administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics
Antihypertensive effect and risk of orthostatic hypotension are increased (additive effect).

Calcium (salts)
Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

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

Corticosteroids, tetracosactide (systemic)
Antihypertensive effect may be decreased (water and 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 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 decrease or even suppression of milk lactation.
Indapamide is not recommended 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 but different reactions related to 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.

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 (≥ 1/10,000, < 1/1000), Very Rare (< 1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.

Metabolism and nutrition disorders
Common: hypokalaemia (see section 4.4).
Uncommon: hyponatraemia (see section 4.4)
Rare: hypochloraemia, hypomagnesaemia.
Very rare: hypercalcaemia.

Nervous system disorders
Rare: vertigo, fatigue, headache, paraesthesia.
Not known: syncope.

Eye disorders
Not known: myopia, blurred vision, visual impairment, acute angle-closure glaucoma, 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 disorders
Uncommon: vomiting.
Rare: nausea, constipation, dry mouth.
Very rare: pancreatitis.

Hepato-biliary disorders

Very rare: abnormal hepatic function.
Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4), hepatitis.

Skin and subcutaneous tissue disorders
Common: hypersensitivity reactions, maculopapular rashes.
Uncommon: purpura.
Very rare: angioneurotic oedema, urticaria, toxic epidermic necrolysis, Steven Johnson syndrome.
Not known: possible worsening of pre-existing acute disseminated lupus erythematosus, photosensitivity reactions (see section 4.4).

Renal and urinary disorders
Very rare: renal failure.

Musculoskeletal and connective tissue disorders
Not known: muscle spasms, muscular weakness, myalgia, rhabdomyolysis.

Reproductive system and breast disorders
Uncommon: erectile dysfunction.

Investigations
Not known: electrocardiogram QT prolonged (see sections 4.4 and 4.5), blood glucose increased (see section 4.4), blood uric acid increased (see section 4.4), elevated liver enzyme levels.

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.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms

Indapamide is not toxic at doses up to 40 mg, i.e. approximately 27 times the therapeutic dose.
Signs of acute poisoning are mostly water/electrolyte balance disturbances (hyponatraemia, hypokalaemia) which are manifested as nausea, vomiting, hypotension, convulsions, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (due to hypovolaemia).

Management

Initial measures involve rapid elimination of the ingested substance by gastric lavage and/or administration of activated charcoal, followed by restoration of water/electrolyte balance in a medical institution.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diuretics;sulfonamides, plain, ATC code: C03BA11.

Mechanism of action

Indapamide is a sulphonamide derivative 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.

Pharmacodynamic effects

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-, mid- 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.

5.2 Pharmacokinetic properties

Indapamide 1.5 mg is supplied in a prolonged-release form.

Absorption
The fraction of indapamide released is rapidly and almost 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. However, variability among individual patients exists.

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

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

Other special populations
The pharmacokinetic parameters of the drug are not significantly changed in patients with renal function impairment.

5.3 Preclinical safety data

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.
The highest doses of indapamide administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of the drug.
The major symptoms of intoxication 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

Hypromellose
Powdered cellulose
Lactose monohydrate
Anhydrous colloidal silica
Magnesium stearate

Film coating
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister (Alu foil, PVC/PVDC foil): 10, 14, 15, 20, 30, 50, 60, 90, 100 prolonged-release tablets in a box.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2023