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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LORVAS SR

(Prolonged-Release Indapamide Tablets B.P.)

COMPOSITION :

Each prolonged release film coated tablet contains :

Indapamide I.P. 1.5 mg

Colour : Titanium Dioxide I.P.

Description :

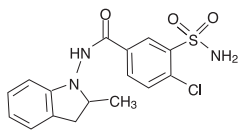
Indapamide is a white to off-white, crystalline powder.

Chemical Name:

4-chloro-N-(2-methyl-1-indolinyl)-3-sulphamoylbenzamide.

Molecular Weight : 365.8

Molecular Formula : $C_{16}H_{16}ClN_3O_3S$



PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMICS

The mechanism whereby Indapamide exerts its action in the control of hypertension is not completely elucidated: both renal and extrarenal actions may be involved. The extrarenal actions involve improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance through:

- 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;

The renal site of action is the proximal part of the distal tubule and the ascending part of Henle's loop. Sodium and chloride ions are excreted in approximately equivalent amounts. The increased delivery of sodium to the distal tubular exchange site results in increased potassium excretion and hypokalemia. As monotherapy, Indapamide sustained release tablets demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity. 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.

Indapamide also reduces left ventricular hypertrophy.

PHARMACOKINETICS

Absorption

The fraction of Indapamide is rapidly and totally absorbed via the gastrointestinal tract. Ingestion with food slightly increases the rate and extent of absorption. Peak serum level following a single dose occurs about 12 hours after ingestion; repeated administration reduces the variation in serum levels between two doses.

Distribution

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80%) and, more specifically, to carbonic anhydrase (98%) without having any significant inhibiting activity on this enzyme. Plasma protein binding is 79%. The plasma elimination half-life is 14 to 24 hours (mean 18 hours). The drug has a volume of distribution of approximately 60 L. Steady state is achieved after 7 days.

Metabolism

Indapamide is extensively metabolized in liver.

Elimination

70% of the dose is eliminated via urinary excretion and 22% via faeces in the form of inactive metabolites. Only 5 to 7 % of the dose is excreted in the urine as unchanged drug.

INDICATIONS

Lorvas SR is indicated in the management of mild to moderate essential hypertension.

CONTRAINDICATIONS

- Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients
- Severe renal failure (< 30 ml/min)
- Hepatic encephalopathy or severe impairment of liver function
- Hypokalaemia

WARNINGS AND PRECAUTIONS :

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. 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 galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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. Any diuretic 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.

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. In this 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 predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal *torsades de pointe.* 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. Frank hypercalcaemia may be due to previously unrecognised hyper parathyroidism. 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. 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 preexisting renal insufficiency.

Athletes: The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, which may give a positive reaction in doping tests

USE IN SPECIFIC POPULATIONS:

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: Breast-feeding is inadvisable (Indapamide is excreted in human milk).

Children and adolescents:

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

ADVERSE REACTIONS

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

Thiazide-related diuretics, including indapamide, may cause the following undesirable effects 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).

Blood and the lymphatic system disorders:

Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Nervous system disorders:

Rare: vertigo, fatigue, headache, paresthesia

Not known: syncope

Cardiac disorders:

Very rare: arrhythmia, hypotension

Not known: Torsade de pointes (potentially fatal)

Gastrointestinal disorders:

Uncommon: vomiting

Rare: nausea, constipation, dry mouth

Very rare: pancreatitis

Renal and urinary disorders:

Very rare: renal failure

Hepato-biliary disorders:

Very rare: abnormal hepatic function

Not known: Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency, Hepatitis

Skin and subcutaneous tissue disorders:

Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:

Common: maculopapular rashes

Uncommon: purpura

Very rare: angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome

Not known: possible worsening of pre-existing acute disseminated lupus erythematosus

Cases of photosensitivity reactions have been reported

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

Metabolism and nutrition disorder

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 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.

Very rare : Hypercalcaemia

Not known: Potassium depletion with hypokalaemia, particularly serious in certain high risk populations, 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.

DRUG INTERACTIONS

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, hydro quinidine, disopyramide)
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics : phenothiazines (chlorpromazine,cyamemazine,levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sultopride, tiapride) and 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). 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 (≥ 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 (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 preexisting 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.

Combinations to 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. 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 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.

Ciclosporin, tacrolimus:

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

Corticosteroids, tetracosactide (systemic route):

Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

DOSAGE AND METHOD OF ADMINISTRATION

One sustained release tablet daily, preferably in the morning. The tablet should be swallowed whole and must not be chewed or crushed. In more severe cases, Lorvas SR can be combined with other categories of anti hypertensive agents like beta-blockers, methyldopa, clonidine, prazosin and ACE inhibitors. 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, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with Indapamide sustained 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: Indapamide sustained release tablet is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

OVERDOSAGE

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 (hypo - natraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, 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.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a dry place at a temperature not exceeding 25^{O}C.

PRESENTATION

Lorvas SR is available as strip pack of 10 tablets.

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Manufactured by :

TORRENT PHARMACEUTICALS (SIKKIM)

32 No. Middle Camp, NH-31A, East District,

Gangtok, Sikkim-737 135.