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

LORVAS

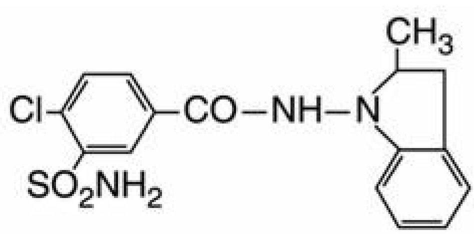
(Indapamide 2.5mg Tablets)

COMPOSITION

Each film coated tablet contains:
Indapamide I.P 2.5 mg
Colour: Lake of Sunset Yellow

DESCRIPTION

Indapamide is an oral antihypertensive/diuretic. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a lipid-soluble methylindoline moiety. It differs chemically from the thiazides in that it does not possess the thiazide ring system and contains only one sulfonamide group. The chemical name of Indapamide is 1-(4-chloro-3-sulfamoylbenzamido)-2-methylindoline, and its molecular weight is 365.84. Indapamide is practically insoluble in water and soluble in ethanol (96%). It is a white or almost white powder.



CLINICAL PHARMACOLOGY

Pharmacodynamics

Indapamide is a non-thiazide indole derivative of chlorosulphonamide belonging to the diuretic family. The mechanism of action of indapamide in hypertensive patients includes reduction in peripheral arterial resistance and normalisation of vascular hyperacivity.

The primary action of indapamide in lowering blood pressure is thought to be due to inhibition of net inward flow of calcium, thereby inhibiting the resultant phasic contractions in vascular smooth muscle.

The antihypertensive effect is also due to the stimulation of the synthesis of prostanglandin PGE_2 and the vasodilator and platelet antiaggregant prostacyclin PGI_2. In addition, the vasodilator action of bradykinin has contributing effect to the over-all vascular mechanism of action of indapamide.

The combined prescription of indapamide with other anti-hypertensives (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.

Pharmacokinetic

Indapamide is rapidly and completely absorbed from the gastro-intestinal tract and peak plasma concentrations are seen 1-2 hours after oral dosing.

Indapamide is concentrated in the erythrocytes and is 79% bound to plasma protein and to erythrocytes. It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility. 70% of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is metabolised to a marked degree with 7% of the unchanged product found in the urine during the 48 hours following administration. Elimination half-life (β phase) of indapamide is approximately 15 - 18 hours.

INDICATIONS

Mild to moderate hypertension

CONTRAINDICATION

- Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients.
- Severe renal failure.
- Anuria.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.
- Recent cerebrovascular accident

WARNINGS AND PRECAUTIONS

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.

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 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. Frank 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 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 pre-existing 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.

DRUG INTERACTION

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).
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 (ACE) inhibitors:
Risk of sudden hypotension and/or acute renal failure when treatment with an ACE inhibitor 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 ACE inhibitor, and restart a hypokalaemic 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 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).

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.

Post-Sympathectomy Patient

The antihypertensive effect of the drug may be enhanced in the post-sympathectomized patient.

Norepinephrine

Indapamide, like the thiazides, may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

ADVERSE EFECTS

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

Cardiac disorders:

Very rare: arrhythmia, hypotension.

Not known: orthostatic hypotension, premature ventricular contractions, irregular heart beats, palpitation

Eye disorders

Not known: Reversible acute myopia

Gastrointestinal disorders:

Uncommon: vomiting

Rare: nausea, constipation, dry mouth, gastric irritation,

Very rare: pancreatitis

Not known: anorexia, dyspepsia, diarrhoea

Hepatobiliary disorders:

Very rare: abnormal hepatic function

Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency, increase in liver enzymes, jaundice (intrahepatic cholestatic jaundice), hepatitis, pancreatitis,

Investigations:

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, increase in plasma uric acid and blood glucose during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes.

At the dosage recommended for hypertension, indapamide does not usually adversely influence plasma triglycerides. LDL cholesterol or the LDL-HDL cholesterol ratio. Indapamide does not appear to adversely affect glucose tolerance when used in patients with or with out diabetes.

Also hyperglycemia,

Metabolism and nutrition

Not known: hyperglycaemia, hyponatraemia, metabolic alkalosis, hypochloremia,

Musculoskelatal and connective tissue disorders:

Not known: muscular cramps, muscular spasm,

Nervous system disorders:

Rare: vertigo, fatigue, headache, paraesthesia, lightheadedness, drowsiness

Not known: dizziness, nervousness, hypertonia, tension,

Renal and urinary disorders:

Very rare: renal failure, increased serum urea nitrogen, or creatinine

Not known: increase in blood urate levels, frequency of urination, polyuria, nocturia, glycosuria

Reproductive disorders

Not known:Impotence, reduced libido

Skin and subcutaneous tissue disorders:

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

Common: maculopapular rashes

Uncommon: purpura, hives, pruritus,

Rare: erythema multiforme, epidermal necrolysis, vasculitis

Very rare: angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome, bullous eruption, Not known: possible worsening of pre-existing acute disseminated lupus erythematosus

Cases of photosensitivity reactions have been reported.

Respiratory system

cough, rhinitis, pharyngitis, sinusitis, conjuctivitis

Other

infection, pain, back pain, asthenia, flu syndrome, abdominal pain, abdominal cramps, chest pain, peripheral edema, weakness, loss of energy, lethargy, tiredness, malaise, numbness of extremities, anxiety, irritability, agitation, rhinorrhea, flushing, weight loss, tingling in extremities, fever, pneumonitis, anaphylaxis reaction, necrotizing angitiis, respiratory distress, sialadenitis, xanthopia.

OVERDOSAGE

Symptoms of overdosage include nausea, vomiting, weakness, gastrointestinal disorders and disturbances of electrolyte balance. In severe instances, hypotension and depressed respiration may be observed. If this occurs, support of respiration and cardiac circulation should be instituted. There is no specific antidote. An evacuation of the stomach is recommended by emesis and gastric lavage after which the electrolyte and fluid balance should be evaluated carefully.

DOSAGES AND ADMINISTRATION

Adults:

The dosage is one tablet, containing 2.5mg indapamide hemihydrate, daily to be taken in the morning.

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:

As for adults.

There are no significant changes in the pharmacokinetics of indapamide in the elderly. Numerous clinical studies have shown that it can be used, without problem and indeed has a particular benefit on systolic blood pressure in the elderly.

Patients with hepatic impairment:

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.

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 indapamide daily is not recommended as there is no appreciable additional antihypertensive 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 antihypertensive agent may be added; those which have been used in combination with indapamide include beta-blockers, ACE inhibitors, methyldopa, clonidine and other adrenergic blocking agents. The co-administration of indapamide with diuretics may cause hypokalaemia and, therefore, is not recommended.

There is no evidence of rebound hypertension on withdrawal of indapamide.

Indapamide tablets are for oral administration only.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

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).

Pediatric Use

Safety and effectiveness of indapamide in pediatric patients have not been established.

Geriatric Use

Clinical studies of indapamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Severe cases of hyponatremia, accompanied by hypokalemia have been reported with recommended doses of indapamide in elderly females.

Expiry date

Do not use later than the date of expiry.

Storage

STORE IN A DRY PLACE AT A TEMPERATURE NOT EXCEEDING 30°C, PROTECTED FROM LIGHT

Presentation

LORVAS is available in Blister strip of 10 Tablets

MARKETED BY

torrent

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