NOVARTIS

Lomir®/Lomir SRO®

Calcium antagonist

COMPOSITION

Lomir

One scored tablet contains:
- Active substance: Isradipine 2.5 mg
- Excipients: Sodium lauryl sulphate, tableting excipients.

Lomir SRO

One low-dose capsule contains:
- Active substance: Isradipine 2.5 mg
- Excipients: Capsule excipients

One capsule contains:
- Active substance: Isradipine 5 mg
- Excipients: Capsule excipients

PROPERTIES/ACTIONS

Isradipine, the active ingredient of Lomir, is a dihydropyridine calcium antagonist with a higher affinity for calcium channels in arterial smooth muscle than for those in the myocardium. It thus dilates arterial vascular beds, in particular those of the heart, brain and skeletal muscle, without depressing cardiac function. As a result of peripheral vasodilation, arterial blood pressure is lowered.
Experiments in animals indicate that isradipine exerts a selective inhibitory action on the sinus node, but does not impair atrioventricular conduction or myocardial contractile function. Therefore, reflex tachycardia is moderate and no prolongation of the PQ interval occurs, even after pre-treatment with a beta-blocker. At blood-pressure-lowering doses isradipine has also been shown to possess a moderate but significant natriuretic activity.
In hypertensive patients a dose-related reduction in supine, sitting and standing blood pressure is achieved within 2–3 hours of a single oral dose. Lomir's long duration of action ensures 24-hour control of arterial blood pressure with once daily administration of two 2.5 mg tablets or one 5 mg SRO capsule; significant lowering of blood pressure is seen after one week of treatment, but at least 3–4 weeks are required for the maximum effect to develop. Changes in heart rate were not normally observed with SRO capsules.
Isradipine was well tolerated when given to patients with hypertension or stable angina pectoris at doses up to 20 or 22.5 mg/day.
Single oral doses of Lomir blunted the bronchospastic response of asthmatic patients to exercise. Lomir has no clinically relevant effect on glucose homeostasis and may therefore be given to diabetic patients.
No cases of orthostatic hypotension have been reported.
No reduction in the antihypertensive effect of Lomir was observed in studies lasting up to 2 years.

PHARMACOKINETICS

Following 90–95% absorption from the gastrointestinal tract, isradipine undergoes extensive first-pass metabolism, resulting in a bioavailability of approx. 20%. Following single oral doses of 2.5–20 mg, the drug is detectable in the plasma within 20 minutes; peak plasma concentrations are reached after approx. 2 hours with the tablet. Healthy volunteers given 5 mg Lomir SRO in the fasting state once daily for 7 days had peak plasma concentrations (C_{max}) of approx. 1.2 ng/ml 6–7 hours after ingestion (t_{max}).
Ingestion of the tablet with food delays the time to peak blood level by about one hour without affecting bioavailability. Ingestion of the SRO capsule with a meal results in slightly higher peak plasma concentrations and increases bioavailability by about 20%. Grapefruit juice increases the bioavailability of dihydropyridines by inhibiting the first-pass effect.
Isradipine is about 95% bound to plasma proteins and its apparent volume of distribution is 283 litres. Both the peak plasma concentration and the area under the curve exhibit a linear relationship with the dose after oral doses of up to 20 mg.
Total clearance of isradipine amounts to 43 l/h.
Elimination is bi-phasic; the terminal half-life is 3.2 hours in younger patients and 8.4 hours in those over 65 years of age. Metabolism is complete, with no unchanged drug being detectable in the urine. About 60–65% of a dose is excreted in the urine and 25–30% in the faeces.
Study data showed no clear evidence of a connection between kidney function and isradipine pharmacokinetics. Both increased and reduced bioavailability have been observed in patients with renal failure. Bioavailability has been reported to be higher in elderly patients and in patients with impaired liver function, reaching values of up to 27%.
For pharmacokinetic interactions see section **Interactions**.

INDICATIONS/POTENTIAL USES

Hypertension

DOSAGE AND ADMINISTRATION

Usual dosage

The recommended dosage for patients with mild to moderate hypertension is one 2.5 mg tablet twice daily or one 5 mg SRO capsule once daily.

Special dosage instructions

Tablets: Treatment should be started with 2.5 mg twice daily. This may be increased progressively at intervals of 4 weeks up to a maximum of 5 mg twice daily. If normal blood pressure levels are still not achieved, the addition of another antihypertensive to the Lomir regimen should be considered.
Capsules: If one 5 mg capsule once daily is not sufficiently effective after at least 4 weeks of treatment, addition of another antihypertensive agent is recommended.
In elderly patients and patients with liver or kidney failure, a starting dose of 1.25 mg (half a tablet) twice daily or one 2.5 mg SRO capsule once daily is recommended.
Lomir can also be added to existing antihypertensive treatment.
When Lomir is given concurrently with cimetidine, the dosage of Lomir should be reduced by 50% (see **Interactions**).
Lomir tablets and SRO capsules must be swallowed whole.

RESTRICTIONS ON USE

Contraindications

Hypersensitivity to dihydropyridines or any of the excipients.
Lomir tablets only: Myocardial infarction less than one month prior to start of therapy, unstable angina pectoris.

Precautions

Extreme caution is advised when giving dihydropyridines to patients with tight aortic stenosis.
Individual dosing of Lomir is recommended in patients with impaired kidney or liver function or chronic heart failure, as well as in the elderly.
Caution should be exercised when treating patients with confirmed or strongly suspected sick sinus syndrome who are not fitted with a pacemaker. Particular care is also recommended in patients with low systolic blood pressure.
There is currently no experience with the use of Lomir or Lomir SRO in patients under 16 years of age.
There is evidence to suggest that, particularly in patients with coronary heart disease, fast-acting calcium antagonists of the dihydropyridine type may cause an increase in cardiovascular morbidity and mortality. Exacerbation of angina pectoris or a sharp fall in blood pressure and tachycardia with unfavourable course may occur during treatment with this product.

Pregnancy / Lactation

Isradipine crosses the placental barrier. Animal data provide no evidence that isradipine has any embryotoxic or teratogenic potential. However, experience with the drug in pregnant women is limited and its use during pregnancy can only be justified if the benefit for the mother clearly outweighs any potential risk to the child. Use of oral Lomir during the third trimester of pregnancy has not been associated with changes in fetal heart rate or uteroplacental blood flow. Antepartal observations in animals suggest that high doses of isradipine may cause prolongation of labour.
A study performed in rats showed that small amounts of isradipine pass into the milk. No studies have been performed in humans. Although animal studies have not revealed any adverse effect of isradipine administered during lactation, the safety of the drug in breast-fed infants has not been demonstrated. Mothers being treated with Lomir should therefore not breast-feed.

ADVERSE EFFECTS

The adverse effects reported most frequently were headache, sensation of heat, facial flushing, localized peripheral oedema of non-cardiac origin, dizziness, palpitations and tachycardia. These effects are related to the vasodilator properties of isradipine and tend to disappear or decrease as treatment continues.
Hypotension is rare.
Non-specific adverse effects, which are rare, include fatigue, rash and gastrointestinal disturbances (nausea, vomiting, diarrhoea).
Elevations of serum transaminases have been observed in a few isolated cases but were reversible either during treatment or following withdrawal.
As with other vasodilatory drugs, angina pectoris may occur in rare instances, particularly in patients with existing coronary heart disease. In patients with existing angina pectoris the frequency, duration and severity of attacks may increase at the start of treatment or as a result of over-rapid dose increments.

INTERACTIONS

Ingestion of the tablets with food does not affect the bioavailability of Lomir, but may delay both the start of absorption and the time to peak plasma concentration by one hour. Ingestion of Lomir SRO capsules with food leads to slightly higher peak plasma concentrations and increases bioavailability by about 20%.
The pharmacokinetic properties of isradipine are not modified by the concomitant administration of digoxin, warfarin, propranolol or hydrochlorothiazide. Isradipine does not affect the kinetics of digoxin, warfarin or hydrochlorothiazide, but does increase the C_{max} and bioavailability (AUC) of propranolol by 58% and 27%, respectively. Isradipine is non-specifically bound to proteins; nevertheless, care is recommended in cases where anticonvulsants are being given concomitantly.
Concomitant use of cimetidine, an inhibitor of the cytochrome P-450 enzyme system, results in an increase of approx. 50% in the bioavailability of isradipine (see **Dosage/Administration**), whereas concomitant administration of rifampicin, known to be a powerful inducer of the cytochrome P-450 enzyme system, greatly reduces the plasma concentrations of isradipine. Concomitant administration of isradipine with rifampicin or with other enzyme-inducing drugs (e.g. phenobarbital) should be avoided.
Isradipine can cause a slight reduction in prothrombin time; however, this is of no clinical significance.
Grapefruit juice inhibits the oxidative degradation of dihydropyridines. Concomitant intake with isradipine may therefore result in increased plasma levels and excessive blood pressure reduction.

OVERDOSE

Experience of isradipine intoxication is limited. The available data suggest that it would result in marked and prolonged hypotension requiring cardiovascular support (e.g. i.v. fluids or plasma volume expanders), with monitoring of cardiorespiratory function and circulating blood volume. Vasoconstrictors may be beneficial, providing their use is not contraindicated. Intravenous calcium may also be tried.

OTHER INFORMATION

Note: Lomir should be kept out of reach of children.

Shelf-life

The drug should not be used after the expiry date (= EXP) printed on the pack.

Manufacturer: See folding box.

Information last revised: July 1998

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Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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