NOVARTIS

Drug Regulatory Affairs

LOMIR SRO® (isradipine)

2.5 and 5 mg modified release (SRO) capsules

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to characterisation of risks and benefits.

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1 Name of the medicinal product

LOMIR SRO® 2.5 and 5 mg modified release (SRO) capsules.

2 Qualitative and quantitative composition

Isradipine is the active substance of Lomir SRO.

2.5 mg and 5 mg SRO capsules

Each 2.5 mg SRO capsule contains 2.5 mg isradipine.

Each 5 mg SRO capsule contains 5 mg isradipine.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Modified release capsules (SRO capsules) for oral administration.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of hypertension.

4.2 Posology and method of administration

The recommended dosage in mild to moderate hypertension is one 5 mg SRO capsule once a day.

Lomir SRO capsules must be swallowed whole.

If one 5 mg SRO capsule once a day is not sufficiently effective after at least 4 weeks of treatment, the addition of another antihypertensive agent is recommended (preferably a thiazide diuretic, ACE inhibitor or beta-blocker).

Lomir SRO can also be added to existing antihypertensive treatment.

When Lomir SRO is given concurrently with cimetidine, the dosage of Lomir SRO should be reduced by 50% (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).

Use in the elderly and in patients with impaired hepatic or renal function

In elderly patients or in patients with impaired hepatic or renal function, a more suitable starting dose is one 2.5 mg SRO capsule once a day.

Use in children

Well designed clinical trials of calcium channel blockers in children have not been performed. Although limited retrospective data are available in the paediatric population, Lomir is not recommended in these patients.

4.3 Contraindications

Known hypersensitivity to isradipine, to other calcium channel blockers of the dihydropyridine type or to any of the excipients (see section 6.1 List of excipients).

As with other calcium channel blockers of the dihydropyridine type, Lomir SRO should not be used in patients with any of the following conditions:

- Cardiogenic shock,
- Unstable angina,
- During or within one month after myocardial infarction.

4.4 Special warnings and precautions for use

Individualized dosing of Lomir SRO is recommended for elderly patients and patients with renal or hepatic dysfunction or chronic heart failure.

Caution should be exercised when treating patients with confirmed or strongly suspected sick sinus syndrome who are not fitted with a pacemaker. Care is recommended when treating patients with low systolic blood pressure.

Extreme caution is advised when giving dihydropyridines to patients with tight aortic stenosis.

Angina pectoris may occur, predominantly in patients with pre-existing coronary artery disease. In patients with pre-existing angina pectoris, frequency, duration and severity of anginal attacks may be increased by rapid dosage increments or at the start of treatment.

Lomir SRO should be discontinued in the event of hypersensitivity to the drug.

Concomitant administration with rifampicin or other enzyme-inducing drugs should be avoided (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs / enzymatic systems on isradipine

Concurrent administration of rifampicin greatly reduces the plasma concentrations of isradipine. Therefore, concomitant administration with rifampicin or other enzyme-inducing drugs (e.g. anticonvulsants such as carbamazepine, phenobarbital) should be avoided.

Based on a case report and on the known risks related to the co-administration of phenytoin with calcium channel blockers, concomitant administration with phenytoin should be avoided.

Increased plasma levels, and potentiation of drug activity and adverse effects (e.g. peripheral oedema), have been reported when dihydropyridines are administered concomitantly with cytochrome P450 3A inhibitors. There is little evidence for such interactions with isradipine, but caution should be exercised when coadministering Lomir with strong CYP3A inhibitors such as macrolide antibiotics (e.g. erythromycin, clarithromycin, troleandomycin), HIV protease inhibitors (e.g. ritonavir, indinavir, nelfinavir) or reverse transcriptase inhibitors (e.g. delavirdine), and azole antifungals (e.g. ketoconazole, itraconazole, voriconazole).

As with all antihypertensives, concomitant treatment with oral baclofen is likely to further increase a possible fall in blood pressure. It may therefore be necessary to monitor blood pressure and adjust the dosage of the antihypertensive medication accordingly.

Concurrent administration of cimetidine increases the bioavailability of isradipine by about 50% (see section 4.2 “Posology and method of administration”).

The peak plasma concentration of isradipine increases by about 20% during co-administration with diclofenac but this is not expected to be clinically significant, as steady state exposure remained unchanged.

The pharmacokinetics of isradipine are not modified by the concomitant administration of digoxin, propranolol, warfarin, hydrochlorothiazide or ciclosporin.

Effects of isradipine on other drugs / enzymatic systems

Isradipine does not seem to inhibit the cytochrome P450 enzymes, in particular CYP3A4, to a clinically significant extent.

Isradipine does not affect the pharmacokinetics of digoxin, warfarin, hydrochlorothiazide, diclofenac, theophylline, triazolam or ciclosporin, but it induces a small (27%) increase in the bioavailability (AUC) of propranolol.

Food interactions

The concomitant intake of grapefruit juice may increase the bioavailability of isradipine.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of pregnant women (63) exposed to Lomir in the third trimester indicate no adverse effects of isradipine on pregnancy or on the health of the fetus or neonate. To date, no other relevant epidemiological data have become available. Animal studies do not show any directly or indirectly harmful effects on pregnancy, embryofetal development, parturition or postnatal development at therapeutically relevant dose levels (see section 5.3 “Preclinical safety data”). The oral use of Lomir in the third trimester has not been associated with any change in fetal heart rate or uteroplacental blood flow and the tocolytic effect seems to be weak.

However, there is insufficient experience with the drug in pregnant women to justify its use during pregnancy unless the benefit to the mother is expected to outweigh any potential risk to the infant.

Lactation

In a study in rats it was shown that small amounts of isradipine pass into the milk. Although animal experiments have not shown isradipine to have any adverse effects when administered during lactation, the safety of the drug in nursing infants has not been established. Women being treated with Lomir SRO should therefore not breast-feed.

4.7 Effects on ability to drive and use machines

There are no data on the effects of Lomir SRO on the ability to drive or use machines. Since, as with other calcium channel blockers, dizziness may occur, especially at the start of treatment, patients should be cautious when driving vehicles or operating machinery.

4.8 Undesirable effects

Most adverse reactions observed in clinical trials were mild, generally dose-dependent and related to the vasodilating properties of Lomir: dizziness, headache, flushing, tachycardia, palpitations and localised peripheral oedema of non-cardiac origin (local arterial dilatation seems to be involved rather than fluid retention). These tend to disappear or to decrease as treatment continues.

Improved tolerability could be achieved with SRO capsules, the incidence of dizziness, headache, flushing and peripheral oedema being lower than with the tablets.

Adverse reactions observed in clinical trials (occurring more frequently with isradipine than with placebo) and compiled from spontaneous reports are presented below according to system organ class.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Blood and the lymphatic system disorders		
	Very rare:	Thrombopenia, leukopenia, anaemia.
Metabolism and nutrition disorders		
	Very rare:	Loss of appetite and anorexia.
Psychiatric disorders		
	Very rare:	Depression, anxiety, nervousness.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness.
	Very rare:	Hypoaesthesia, paraesthesia, somnolence.
Eye disorders		
	Very rare:	Visual disturbance, blurred vision.
Cardiac disorders		
	Common:	Tachycardia, palpitations.
	Very rare:	Ventricular arrhythmia, myocardial infarction, heart failure, angina pectoris, atrial fibrillation, bradycardia.
Vascular disorders		
	Very common:	Flushing, peripheral oedema.
	Uncommon:	Hypotension.
Respiratory, thoracic and mediastinal disorders		
	Common:	Dyspnoea
	Very rare:	Cough.
Gastrointestinal disorders		
	Common:	Abdominal discomfort.
	Very rare:	Vomiting, nausea, gingival hyperplasia.
Hepato-biliary disorders		
	Very rare:	Elevation in liver function tests, isolated cases of hepatitis.
Skin and subcutaneous tissue disorders		
	Common:	Rash.
	Very rare:	Allergic skin reaction, pruritus, sweating, anaphylactic reactions and angioedema, isolated cases of photosensitivity.
Musculoskeletal, connective tissue and bone disorders		
	Very rare:	Arthralgia, back pain, muscle cramps, pain in limbs.
Renal and urinary disorders		
	Common:	Polyuria.
Reproductive system and breast disorders		
	Very rare:	Erectile dysfunction, isolated cases of gynecomastia.
General disorders and administration site conditions		
	Common:	Fatigue, malaise.
	Very rare:	Asthenia.
Investigations		
	Uncommon:	Weight increased.

The following adverse events of unknown frequency have been reported during post-approval use of Lomir: stroke, syncope, transient ischaemic attack, lethargy, dry mouth, constipation, diarrhea, insomnia, chest pain.

4.9 Overdose

Experience with Lomir overdosage is limited. The available data suggest that overdosage might result in marked and prolonged hypotension requiring cardiovascular support (e.g. i.v. fluids or plasma volume expanders), with monitoring of both cardiorespiratory function and circulating blood volume. Vasoconstrictors may be beneficial, provided their use is not contraindicated. Calcium i.v. may also be tried.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives; ATC code: C08C A03.

Isradipine, the active substance of Lomir SRO, is a potent dihydropyridine calcium channel blocker with selective activity on voltage-gated calcium channels (L-type or “long acting”). Isradipine has a higher affinity for such 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 and in man indicate that isradipine exerts a minimal depressant activity on the sinoatrial node automaticity, but does not impair atrioventricular conduction or myocardial contractile function. Reflex tachycardia is therefore moderate and no prolongation of the P-Q interval occurs, even after pretreatment with a β-blocker. Isradipine, at blood pressure lowering doses, has also been shown to possess moderate but significant natriuretic activity in animals and man and to exert an anti-atherogenic effect in animals.

Treatment with isradipine slightly increases renal plasma flow and glomerular filtration rate, slightly decreases renal vascular resistance during the first 3 to 6 months of therapy. These changes were not maintained after 1 year of treatment but renal function was preserved in comparison to untreated hypertensive patients. Treatment with isradipine produces a sustained natriuretic and diuretic effect, which contributes to its antihypertensive effect. Calcium channel blockers have also exerted a renal protective effect in renal transplant patients receiving ciclosporin. Afferent arteriolar dilatation in particular seems to play a significant role there.

In hypertensive patients, a dose-related reduction in supine, sitting and standing blood pressure is achieved within 2 to 3 hours of administration of a single tablet. In therapeutic use, Lomir's long duration of action ensures 24-hour control of arterial blood pressure with once daily administration of an SRO capsule. Significant lowering of blood pressure is seen after one week of treatment, but at least 3 to 4 weeks are required for the maximum effect to develop. Changes in heart rate have not usually been observed with SRO capsules.

Lomir has been well tolerated when given at doses of up to 20 and 22.5 mg/day to patients with hypertension or stable angina pectoris.

Single oral doses of Lomir blunted the bronchospastic response of asthmatic patients to exercise.

Because it has no clinically relevant effect on glucose homoeostasis, isradipine may be given to diabetic patients.

No diminution of the antihypertensive effect of Lomir occurred in studies lasting up to 2 years.

5.2 Pharmacokinetic properties

Absorption

After 90 to 95% absorption from the gastrointestinal tract, Lomir undergoes extensive first-pass metabolism resulting in a bioavailability of about 16 to 18%.

After doses of up to 20 mg, both the peak plasma concentration and the area under the curve exhibit a linear relationship with the dose.

About 50% of the isradipine contained in Lomir SRO capsules is absorbed within 10 hours, and the peak plasma concentration is reached approximately 5 to 7 hours after administration. The peak plasma concentration (C_{max}) is 1 ng/mL for a single dose 5 mg SRO capsules and 1.8 ng/mL at steady state.

Ingestion of the SRO capsule with food leads to slightly higher peak plasma concentrations and increases the bioavailability of Lomir SRO by about 20%.

Distribution

Isradipine is about 95% bound to plasma proteins and its apparent distribution volume is 283 L.

Biotransformation

Isradipine is extensively biotransformed in the liver by deesterification and aromatisation of the dihydropyridine moiety. Five metabolites of isradipine account for 95% of the dose of the parent compound. In vitro none of these metabolites contribute to the cardiovascular effects of isradipine. No unchanged drug has been detectable in the urine.

Elimination

The total clearance of Lomir is 43 L/hour. Its elimination is biphasic, with a terminal half-life of 8.4 hours. About 60 to 65% of an administered dose is excreted in the urine and 25 to 30% in the faeces.

Special populations

Data have shown no clear correlation between renal function and pharmacokinetics, both an increase and a decrease in bioavailability having been observed in patients with impaired renal function. Bioavailability has been reported to be higher in elderly patients and in patients with impaired liver function, reaching values of up to 27%.

5.3 Preclinical safety data

Preclinical data - based on conventional studies of single and multiple dose toxicity and of genotoxic, clastogenic or carcinogenic potential - reveal no special hazard for humans. Embryotoxicity was noted only at maternally toxic doses. Isradipine has no teratogenic potential.

6 Pharmaceutical particulars

6.1 List of excipients

Cellulose, microcrystalline; cetyl palmitate; gelatine; iron oxide, black (only for Lomir 2.5 mg SRO); iron oxide, red (only for Lomir 5 mg SRO); iron oxide, yellow; magnesium stearate; methylhydroxypropylcellulose; shellac; silica, colloidal anhydrous; titanium dioxide.

Information might differ in some countries

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months worldwide.

Information might differ in some countries.

6.4 Special precautions for storage

Store below 30°C.

Information might differ in some countries.

Lomir SRO must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Alu/ PVC/PVDC or two-sided aluminium (Alu/Alu) blister packs.

Country specific.

6.6 Special precautions for handling

No special requirements.