SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prescal Tablets 2.5mg.
Isradipine 2.5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5mg isradipine INN

Excipients: each tablet contains 74.4 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow circular flat bevelled edge, angle scored tablets, 6mm in diameter, marked HL on one side and SANDOZ on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prescal is recommended for the treatment of essential hypertension

4.2 Posology and method of administration

Route of administration: oral

Prescal can be administered with or without food.

The recommended dosage is 2.5 mg twice a day (i.e. about every 12 hours). Treatment for 3-4 weeks is required for the maximum effect to develop. If blood pressure is not adequately controlled after this period patients may require a dosage of 5 mg twice a day, or if more appropriate, the addition of a low dose of another anti-hypertensive agent i.e. thiazide diuretic, ACE inhibitor or beta-blocker. Exceptionally some patients may require up to 10mg twice a day. Prescal can also be added to an ongoing regimen of other anti-hypertensive agents.

Use in the elderly and in patients with hepatic dysfunction:
In elderly patients or in patients with hepatic dysfunction, a more suitable starting
dose is 1.25 mg (1/2 tablet) twice a day for hypertension. However, the dosage may
be increased according to the requirements of the individual patient. Once daily
maintenance treatment with 2.5 mg or 5 mg may be sufficient in some hypertensive
patients.

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, Prescal 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 should not
be used in patients with any of the following conditions:
• Cardiogenic shock,
• Unstable angina,
• During or within one month after myocardial infarction.
• Treatment of hypertensive crisis

4.4 Special warnings and precautions for use

Individual dosing is recommended for the elderly and patients with hepatic
dysfunction (see section 4.2 “Posology and method of administration”).

A cautious dosing regimen is recommended for patients with renal dysfunction or
chronic heart failure.

As for other calcium antagonists Prescal does not give protection against the danger
of abrupt beta-blocker withdrawal. Beta-blockers should therefore be withdrawn
gradually, preferably over 8-10 days.

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.

Prescal should be used with caution in patients with poor cardiac reserve.

Extreme caution is advised when giving dihydropyridines to patients with severe
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.
There is no evidence that Prescal interferes with glucose metabolism, however, diabetic patients should be initially monitored in accordance with good clinical practice.

Prescal should be discontinued in the event of hypersensitivity to the drug.

Prescal tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, a special form for hereditary lactase deficiency (Lapp lactase deficiency) or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs and/or enzymatic system 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 and phenobarbital) should be avoided.

Based on an isradipine 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 co-administering Prescal 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%. When Prescal is given concurrently with cimetidine, the dosage of Prescal should be reduced by 50%.

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 and/or enzymatic systems:
Prescal 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 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of pregnant women (63) exposed to Prescal 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 Prescal 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. Pre-natal observations in animals suggest that high doses of isradipine may cause prolongation of labour.

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.

Breast-feeding
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 Prescal should therefore not breast-feed.

4.7 Effects on ability to drive and use machines

There are no data on the effects of Prescal on the ability to drive or use machines. As with other calcium channel blockers, syncope, dizziness, hypotension, visual disturbances and blurred vision are known adverse reactions associated with the use of Prescal. Patients should not drive a vehicle or operate a machine or perform tasks that require alertness if they experience these symptoms.

4.8 Undesirable Effects

Most adverse reactions observed in clinical trials were mild, generally dose dependent and related to the vasodilating properties of Prescal: headache, flushing, dizziness, 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.

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; not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

<table>
<thead>
<tr>
<th><strong>Blood and the lymphatic system disorders</strong></th>
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<tbody>
<tr>
<td>Very rare: Thrombocytopenia, leukopenia, anaemia.</td>
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<th><strong>Immune system disorders</strong></th>
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<tr>
<td>Very rare: Anaphylactic reactions</td>
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<tr>
<th><strong>Metabolism and nutrition disorders</strong></th>
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<tbody>
<tr>
<td>Very rare: Decreased appetite</td>
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<tr>
<th><strong>Psychiatric disorders</strong></th>
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<tr>
<td>Very rare: Depression, anxiety, nervousness</td>
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<tr>
<td>Not known: Insomnia</td>
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<tr>
<th><strong>Nervous system disorders</strong></th>
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<tbody>
<tr>
<td>Very common: Headache</td>
<td></td>
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<tr>
<td>Common: Dizziness</td>
<td></td>
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<tr>
<td>Very rare: Hypoesthesia, paraesthesia, somnolence</td>
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</tr>
<tr>
<td>Not known: Transient ischemic attack, lethargy, syncope, stroke</td>
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<th><strong>Eye disorders</strong></th>
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<tr>
<td>Very rare: Visual impairment, vision blurred</td>
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<th><strong>Cardiac disorders</strong></th>
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<tbody>
<tr>
<td>Common: Tachycardia, palpitations</td>
<td></td>
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<tr>
<td>Very rare: Ventricular arrhythmia, myocardial infarction, cardiac failure, angina pectoris, atrial fibrillation, bradycardia</td>
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<thead>
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<th><strong>Vascular disorders</strong></th>
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<tr>
<td>Very common: Flushing</td>
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<tr>
<td>Uncommon: Hypotension</td>
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<tr>
<th><strong>Respiratory, thoracic and mediastinal disorders</strong></th>
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<tbody>
<tr>
<td>Common: Dyspnoea</td>
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<tr>
<td>Very rare: Cough</td>
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<th><strong>Gastrointestinal disorders</strong></th>
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<tr>
<td>Common: Abdominal discomfort</td>
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<tr>
<td>Very rare: Vomiting, nausea, gingival hyperplasia</td>
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</tbody>
</table>
Not known: Dry mouth, constipation, diarrhea

**Hepato-biliary disorders**
Very rare: Hepatitis

**Skin and subcutaneous tissue disorders**
Common: Rash
Very rare: Dermatitis allergic, pruritus, hyperhidrosis, angioedema, and photosensitivity reaction

**Musculoskeletal and connective tissue disorders**
Very rare: Arthralgia, back pain, muscle spasms, pain in extremities

**Renal and urinary disorders**
Common: Polyuria

**Reproductive system and breast disorders**
Very rare: Erectile dysfunction, gynecomastia.

**General disorders and administration site conditions**
Very common: Oedema peripheral
Common: Fatigue, malaise
Very rare: Asthenia
Not known: Chest pain

**Investigations**
Uncommon: Weight increased
Very rare: Elevation in liver function tests

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**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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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**4.9. Overdose**

*Symptoms*
Experience with Prescal overdosage is limited. The available data suggest that overdosage might result in marked and prolonged hypotension

*Management*
Patients should be admitted to hospital and generally should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate.

Animal data suggest the risk for cardio-depression with Prescal should be minimal, but depression of the sinus node may occur in which case temporary pacemaker treatment may be useful.

In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage and/or activated charcoal to remove the drug from the gastrointestinal tract (only if presented within 1 hour after ingestion of Prescal).

Since isradipine is bound to plasma proteins to a very large extent, dialysis cannot be expected to be of benefit.

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives.

ATC code: C08C A03.

Isradipine is a dihydropyridine calcium antagonist with a higher affinity for calcium channels in arterial smooth muscle than for those in the myocardium. Thus it produces vasodilation of peripheral coronary and cerebral arteries without notably depressing cardiac function. As a result of the vasodilation of peripheral arteries, the arterial blood pressure is lowered; the attending afterload reduction improves myocardial contractility and increases cardiac output, while myocardial oxygen consumption decreases. In animal studies isradipine has been observed to exert a cardioprotective effect against ischaemic injury without cardiodepression.

5.2 Pharmacokinetic properties

Following oral administration of Prescal, isradipine is completely absorbed (90-95%) from the gastro-intestinal tract and undergoes extensive first pass metabolism resulting in a bioavailability of 15-24%. Single oral doses are detectable in the plasma within 20 minutes and peak plasma concentrations are reached approximately 2 hours after intake. Isradipine is approximately 95% bound to plasma proteins.

The bioavailability of isradipine is not affected by co-administration of food. However, the lag time to absorption and time to peak plasma concentration may be delayed by about one hour.
No clear correlation between renal function and pharmacokinetic parameters has been found; both an increase and a decrease in bioavailability has been observed in patients with impaired renal function. The bioavailability of isradipine was increased in elderly patients with impaired renal function.

5.3 Preclinical safety data

Preclinical data, based on studies in the rat and rabbit, reveal no special hazards for humans for teratogenicity or embryotoxicity (see section 4.6 for possible prolongation of labour). Animal studies do not show any harmful effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium lauryl sulphate, magnesium stearate, povidone, maize starch, lactose monohydrate, purified water.

6.2 Incompatibilities

None.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Protect from light. Store below 30°C.

Prescal must be kept out of the reach and sight of children.

6.5 Nature and contents of container

56 or 60 tablets in White opaque PVC/PVdC blister pack in outer box cardboard container; PVC 250 micron, PVdC 60 GSM, Aluminium foil 20 micron.
56 or 60 tablets in Red transparent PVC/PVdC blister pack in outer box cardboard container; PVC 200 micron, PVdC 60 GSM, Aluminium foil 20 micron.

6.6 Instructions for use/handling
None

7 MARKETING AUTHORISATION HOLDER
Novartis Pharmaceuticals UK Limited
Trading as Ciba Laboratories
Frimley Business Park
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Surrey
GU16 5SG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00101/0537

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17 November 1997

10 DATE OF REVISION OF THE TEXT
29/05/2014