NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DYNACIRC SRO® 2.5mg Modified Release (SRO) Capsules

DYNACIRC SRO® 5mg Modified Release (SRO) Capsules

(Isradipine)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- One 2.5mg Modified Release (SRO) Capsule contains 2.5 mg of isradipine
- One 5 mg Modified Release (SRO) Capsule contains 5 mg of isradipine

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

2.5 mg and 5 mg modified release capsules (SRO capsules) for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypertension.

4.2 Dose and method of administration

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

Dynacirc 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).

Dynacirc SRO can also be added to existing antihypertensive treatment.

When Dynacirc SRO is given concurrently with cimetidine, the dose of Dynacirc SRO should be reduced by 50% (see section 4.5 Interactions with other medicines and other forms of interaction).

Special Populations

Geriatrics, renal impairment and hepatic impairment

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.

Paediatrics

Well designed clinical trials of calcium channel blockers in children have not been performed. Although limited retrospective data are available in the paediatric population, Dynacirc 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, Dynacirc 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 Dynacirc SRO is recommended for elderly patients and patients with hepatic impairment.

A cautious dosing regimen is recommended for patients with renal impairment 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 severe aortic stenosis.

Angina pectoris may occur, predominantly in patients with pre-existing coronary artery disease. At the start of treatment or when dosage increments are made too quickly in patients with pre-existing angina pectoris, frequency, duration and severity of anginal attacks may be increased.

If hypersensitivity develops, Dynacirc SRO should be discontinued.

Concomitant administration with rifampicin or other enzyme-inducing drugs should be avoided (see section 4.5 Interactions with other medicines and other forms of interaction).

4.5 Interactions with other medicines and other forms of interaction

Interactions resulting in a concomitant use not recommended

Effects of other drugs / enzymatic systems on isradipine

Anticonvulsant drugs

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.

Interactions to be considered

Antimicrobial drugs

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 Dynacirc 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).

Antihypertensive drugs

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.

Cimetidine

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

NSAIDS

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.

Isradipine induces a small (27%) increase in the bioavailability (AUC) of propranolol. The clinical relevance is not known.

Food interactions

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

4.6 Fertility, Pregnancy and lactation

Women of child-bearing potential

There are no data supporting any special recommendations in women of child-bearing potential.

Fertility

Animal studies do not show any harmful effects on fertility (see Section 5.3 Pre-clinical safety data).

Pregnancy

There is limited information on the use of Dynacirc SRO in pregnant women. Data on a limited number of pregnant women exposed to Dynacirc in the third trimester indicate no adverse effects of isradipine on pregnancy or on the health of the fetus or neonate. 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 Pre-clinical safety data). The oral use of Dynacirc

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.

The risk to the fetus/mother is unknown. Because animal reproductive toxicity studies are not always predictive of human response, isradipine should be used during pregnancy only if clinically indicated and only if the expected benefit outweighs the potential risk to the fetus.

Lactation

There is limited information on the use of Dynacirc SRO in breast-feeding women. In a study in rats it was shown that small amounts of isradipine pass into the milk. Animal experiments have not shown isradipine to have any adverse effects when administered during lactation. It is unknown whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isradipine is administered to a breastfeeding woman.

4.7 Effect on ability to drive and use machines

There are no data on the effects of Dynacirc SRO 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 drug reactions associated with the use of Dynacirc. 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 Dynacirc: 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 oedema peripheral being lower than with the tablets.

Adverse drug reactions (Table 1) are listed according to system organ class in MedDRA. MedDRA version used is 15.1. *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 1 **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**

Blood and the lymphatic system disorders		
	Very rare:	Thrombocytopenia, leukopenia, anaemia.
Immune system disorders		
	Very rare:	Anaphylactic reactions
Metabolism and nutrition disorders		
	Very rare:	Decreased appetite.
Psychiatric disorders		
	Very rare:	Depression, anxiety, nervousness.

Not known:	Insomnia.

Nervous system disorders

Very common:	Headache.
Common:	Dizziness.
Very rare:	Hypoaesthesia, paraesthesia, somnolence.
Not known:	Transient ischemic attack, lethargy.
Not known:	Syncope, stroke

Eye disorders

Very rare:	Visual impairment, vision blurred.

Cardiac disorders

Common:	Tachycardia, palpitations.
Very rare:	Ventricular arrhythmia, myocardial infarction, cardiac failure, angina pectoris, atrial fibrillation, bradycardia.

Vascular disorders

Very common:	Flushing.
Uncommon:	Hypotension.

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea
Very rare:	Cough.

Gastrointestinal disorders

Common:	Abdominal discomfort.
Very rare:	Vomiting, nausea, gingival hyperplasia.
Not known:	Dry mouth, constipation, diarrhoea.

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 extremity.
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:	Liver functions test abnormal

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Signs and Symptoms: Experience with Dynacirc SRO overdosage is limited. The available data suggests that overdosage might result in marked and prolonged hypotension.

Treatment: 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.

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 Dynacirc).

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

For advice on the management of overdose please contact the National Poisons Centre 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics (PD)

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

Isradipine, the active substance of Dynacirc, 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, Dynacirc's long duration of action ensures 24-hour control of arterial blood pressure with twice daily administration of tablets or 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.

With tablets, increases in the resting heart rate are minimal (less than 5 beats/minute) and not dose-dependent.

Changes in heart rate have not usually been observed with SRO capsules.

Dynacirc 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 Dynacirc 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 Dynacirc occurred in studies lasting up to 2 years.

Clinical studies

Dynacirc SRO is an established product.

5.2 Pharmacokinetics (PK)

Absorption

After 90 to 95% absorption from the gastrointestinal tract, Dynacirc 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 Dynacirc 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 Dynacirc SRO by about 20%.

Distribution

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

Metabolism

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 data showed that none of these metabolites contribute to the cardiovascular effects of isradipine.

Elimination

The total clearance of Dynacirc SRO 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 as metabolites. No unchanged drug has been detectable in the urine.

Special populations

Renal impairment

Data have shown no clear correlation between renal function and bioavailability, both an increase and a decrease in creatinine clearance and systemic clearance of isradipine has been observed in patients with impaired renal function.

Elderly and Hepatic impairment

Bioavailability has been reported to be higher in elderly patients and in patients with impaired liver function, reaching increases of up to 27%.

5.3 Pre-clinical safety data

Preclinical data - based on conventional studies of single and multiple dose toxicity reveal no special hazard for humans. There is no genotoxic, clastogenic or carcinogenic potential. Animal studies do not show any harmful effects on fertility**.** Embryotoxic effects were noted only at maternally toxic doses. There was no evidence of teratogenicity of isradipine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose,

microcrystalline;

cetyl palmitate;

gelatine;

iron oxide,

black (only for Dynacirc 2.5 mg SRO);

iron oxide, red (only for Dynacirc 5 mg SRO);

iron oxide, yellow;

magnesium stearate;

hypromellose

shellac;

silica,

colloidal anhydrous;

titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

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

6.5 Nature and contents of container

Alu/PVC/PVDC blister pack containing 10 or 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for handling

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Novartis New Zealand Limited

PO Box 99102
Newmarket

Auckland 1149
Telephone: 0800 354 335

® Registered trademark of Novartis

9 DATE OF FIRST APPROVAL

30 May 1991

10 DATE OF REVISION OF THE TEXT

08 September 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 8 - SPONSOR	Removed Sponsor's old address.

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