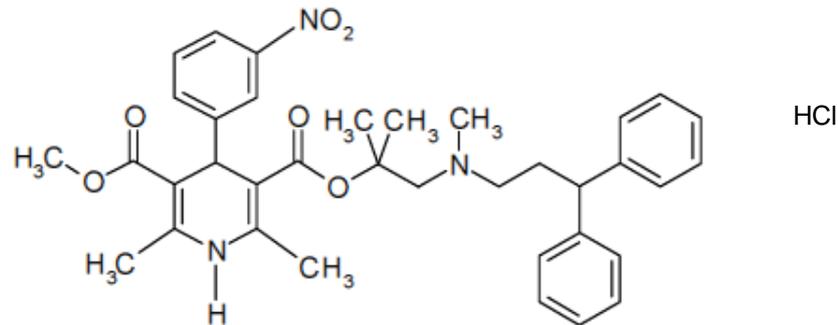


**APO-LERCANIDIPINE TABLETS****NAME OF THE MEDICINE**

Lercanidipine Hydrochloride.

Chemical Name: 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride.

Structural Formula:

Molecular Formula:  $C_{36}H_{42}ClN_3O_6$ 

Molecular Weight: 648.2 (free base: 611.7)

CAS Registry Number: 132866-11-6

**DESCRIPTION**

Lercanidipine is a dihydropyridine derivative. It is a racemate due to the presence of a chiral carbon atom at position 4 of the 1,4-dihydropyridine ring.

Lercanidipine hydrochloride is a yellow amorphous powder, readily soluble in chloroform and methanol, practically insoluble in water. Octanol:water partition coefficient (LogP): 6.4.

Each tablet contains lercanidipine hydrochloride as the active ingredient. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose, croscarmellose sodium, butylated hydroxytoluene, magnesium stearate, hypromellose, macrogol 8000, titanium dioxide, purified talc, yellow iron oxide (10 mg only) and red iron oxide (20 mg only).

**PHARMACOLOGY****Pharmacological Actions**

Lercanidipine is a calcium antagonist of the dihydropyridine group and selectively inhibits the transmembrane influx of calcium into cardiac and vascular smooth muscle, with a greater effect on vascular smooth muscle than on cardiac smooth muscle. The antihypertensive action is due to a direct relaxant effect on vascular smooth muscle which lowers total peripheral resistance and hence blood pressure. Lercanidipine has a prolonged antihypertensive activity because of its high membrane partition coefficient. It is devoid of negative inotropic effects and its vascular selectivity is due to its voltage dependent calcium antagonist activity. Since the vasodilatation induced by lercanidipine hydrochloride is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.

As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to the (S)-enantiomer. No significant effects on ECG have been seen.

**Pharmacokinetics****Absorption**

Lercanidipine is completely absorbed after oral administration. Peak plasma levels of  $3.30 \text{ ng/mL} \pm 2.09 \text{ s.d}$  and  $7.66 \text{ ng/mL} \pm 5.90 \text{ s.d}$  occur 1.5-3 hours after dosing with 10 mg and 20 mg, respectively. The absolute bioavailability of lercanidipine is about 10%, because of high first pass metabolism. The bioavailability increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal, and about 2-fold when taken immediately after a carbohydrate-rich meal. Consequently, lercanidipine should

be taken at least 15 minutes before a meal.

With oral administration, lercanidipine exhibits non-linear kinetics. After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, showing a progressive saturation of first pass metabolism. Accordingly, bioavailability increases as dosage increases. The two enantiomers of lercanidipine have a similar time to peak plasma concentration. The peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S)-enantiomer. No *in vivo* interconversion of enantiomers is observed.

#### Distribution

Distribution of lercanidipine from plasma to tissues and organs is rapid and extensive. Serum protein binding exceeds 98%. The free fraction of lercanidipine may be increased in patients with renal or hepatic impairment as plasma protein levels are decreased in these disease states.

#### Metabolism

As for other dihydropyridine derivatives, lercanidipine is extensively metabolised by CYP3A4. It is predominantly converted to inactive metabolites; no parent drug is found in the urine or faeces. About 50% of the dose is excreted in the urine.

#### Elimination

The mean terminal elimination half-life of S- and R-lercanidipine enantiomers is  $5.8 \pm 2.5$  and  $7.7 \pm 3.8$  hours, respectively. No accumulation was seen upon repeated administration. The therapeutic activity of lercanidipine lasts for 24 hours, due to its high binding to lipid membranes.

#### Elderly Patients

In elderly patients, the pharmacokinetics of lercanidipine are similar to those observed in the general population.

#### Hepatic Impairment

A study in patients with mild hepatic impairment (Child-Pugh class A) showed that the pharmacokinetic behaviour of the drug is similar to that observed in the general population. No studies have been undertaken in patients with moderate or severe hepatic impairment.

#### Renal Impairment

In patients with severe renal dysfunction (creatinine clearance < 12 mL/min) or dialysis dependent patients, plasma levels were increased by about 70%. As a consequence, the drug should be contraindicated in severe renal impairment.

## **CLINICAL TRIALS**

### **Placebo-Controlled Studies**

Lercanidipine has been compared to placebo in four (4) to 16-week studies, involving 671 patients with mild-moderate essential hypertension. All studies used a 3-week placebo run-in period. End-points were diastolic and systolic blood pressure 24 hours post dose. Both 10 mg and 20 mg once daily significantly lowered diastolic and systolic blood pressure compared to placebo, and the reduction in blood pressure was maintained throughout the 24 hour dosing period.

Diastolic blood pressure changes observed after 4-week treatment with 10-20 mg daily lercanidipine ranged between 8 and 13 mmHg, as compared to 3-6 mmHg induced by placebo.

Studies with 24-hour ambulatory blood pressure monitoring have documented that the antihypertensive effect of lercanidipine is maintained throughout the 24 hour dosing period, with limited variations between peak (5-7 hours post dosing) and trough blood pressure changes.

### **Active-Controlled Studies**

Four clinical trials involving 538 patients with mild-moderate essential hypertension have compared lercanidipine with nifedipine SR, atenolol, hydrochlorothiazide and captopril. Trials included a 2-week washout period followed by a 3-week placebo run-in, and 12-16 weeks of active treatment. Diastolic and systolic blood pressure was measured 24 hours post-dose. Lercanidipine was as effective as the comparator drugs, and at least as well tolerated. 24-hour blood-pressure monitoring was used in a comparative, cross-over trial of lercanidipine versus amlodipine (n = 16). The effect of lercanidipine paralleled that of amlodipine throughout the 24 hour period.

### **Patients with Isolated Systolic Hypertension**

The effect of lercanidipine 10-20 mg daily on isolated systolic hypertension was studied in a double-blind, randomised, placebo-controlled study in 83 elderly patients (sitting SBP > 160 mmHg and sitting

DBP < 95 mmHg). The study consisted of 1 week wash-out, 3 weeks placebo run-in, and 8 weeks of active treatment. Systolic and diastolic blood pressure was measured 24 hours post dose. Lercanidipine 10 to 20 mg was efficacious in lowering systolic blood pressure from the initial values of  $172.6 \pm 5.6$  mmHg to  $140.2 \pm 8.7$  mmHg (mean  $\pm$  SD, per-protocol population in all patients completing the whole 8 weeks of double-blind treatment), as compared to the changes in the placebo group (from  $172.4 \pm 6.3$  to  $162.8 \pm 9.7$  mmHg). Therefore, at study endpoint, patients treated with lercanidipine experienced a significantly greater decrease ( $-22.6$  mmHg,  $p < 0.001$ ) in sitting systolic blood pressure in comparison to placebo. The diastolic blood pressure was within normal range.

### Long-Term Studies

In long term studies, 399 patients were followed for 12 months, with dose titration allowed every 4 weeks, to 30 mg daily. Development of tolerance was not seen. The antihypertensive effect was maintained, and the heart rate was not significantly affected. A further fall in blood pressure was seen after the first and second month, with blood pressure stabilising in the third month. The majority of patients remained on 10 mg once daily.

## INDICATIONS

Lercanidipine is indicated for the treatment of hypertension.

## CONTRAINDICATIONS

- Known hypersensitivity to lercanidipine, any dihydropyridine or any other ingredient in APO-Lercanidipine tablets (see **PRESENTATION AND STORAGE CONDITIONS**);
- Severe hepatic impairment;
- Severe renal impairment (creatinine clearance <12 mL/min);
- Concomitant treatment of APO-Lercanidipine tablets with cyclosporin should be avoided.

## PRECAUTIONS

### Ischaemic Heart Disease

It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine is long-acting, caution should be required in such patients.

### Outflow Obstruction (Aortic Stenosis)

Lercanidipine should be administered with caution in patients with left ventricular outflow obstruction (aortic stenosis).

### Congestive Heart Failure

In general calcium channel blockers should be used with caution in patients with heart failure. Although animal data and acute haemodynamic evaluation in patients with preserved left ventricular function have not demonstrated that lercanidipine exerts a direct negative inotropic effect, safety in patients with congestive heart failure has not been established. Therefore, as for other calcium channel blockers, lercanidipine should be used with caution in such patients, especially if untreated.

### Unstable Angina Pectoris or within one month of a Myocardial Infarction

Rarely patients have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase (particularly those with severe obstructive coronary artery disease). The mechanism of this effect has not been elucidated; however the possibility of an exacerbation of angina and/or cardiac ischaemia exists. It is therefore suggested that the use of calcium channel blockers is not advisable in patients with unstable angina pectoris or recent myocardial infarction.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence for genotoxic activity was observed with lercanidipine in *in vitro* assays of gene mutation (reverse mutation in *S. Typhimurium*, forward mutation in Chinese Hamster V79 fibroblasts), gene conversion (in *Saccharomyces cerevisiae* D4) or chromosomal damage (CHO cytogenetic assay). Negative findings were also obtained with lercanidipine in an *in vivo* assay of chromosomal damage (mouse micronucleus test).

Carcinogenicity studies of lercanidipine (administered via the diet) have been performed in rats and mice (18 months), using doses up to 60 mg/kg/day for mice and 5 mg/kg/day for rats. Plasma concentrations (AUC) of lercanidipine at the highest doses used in these studies were about 2-4 times the highest AUC expected in humans during treatment with lercanidipine. Lercanidipine showed no evidence of carcinogenic activity in these studies.

Administration of lercanidipine at oral doses up to 12 mg/kg/day (associated with plasma lercanidipine concentration (AUC) about 20-40 times higher than the expected human AUC) had no effect in male or female fertility in rat.

### **Use in Pregnancy (Category C)**

*Category C - Definition: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

There is no clinical experience with lercanidipine in pregnancy, but other dihydropyridine compounds have been found to cause irreversible malformations in animals. Therefore, lercanidipine should not be administered during pregnancy or to women with childbearing potential unless effective contraception is used.

In animal studies, pregnant rats given lercanidipine orally at doses  $\geq$  2.5 mg/kg/day, beginning prior to mating, or 12 mg/kg/day, beginning from early gestation, showed signs of distocia and had an increased incidence of still births and a lower neonatal survival index. The no-effect dose for effects on parturition and neonatal survival was 0.5 mg/kg/day (associated with lercanidipine concentration (AUC) about 50% of the expected human AUC) when dosing started before pregnancy or 2.5 mg/kg/day (about 3 times the human AUC) when dosing started during early gestation. Administration with lercanidipine at doses of 2.5 mg/kg/day during gestation also caused a higher incidence of foetal visceral abnormalities (mono/bilateral renal pelvic and/or ureteric dilatation) and skeletal abnormalities (mainly delayed ossification) at all dose levels. A no-effect dose was not established. The effects of lercanidipine during pregnancy have not been investigated adequately in a non-rodent species.

### **Use in Lactation**

There is no clinical experience with lercanidipine in lactation. Distribution into milk may be expected, due to the high lipophilicity of lercanidipine. Therefore, lercanidipine should not be administered to lactating women.

### **Paediatric Use**

Due to lack of clinical experience, lercanidipine is not recommended for use in patients under the age of 18.

### **Use in the Elderly**

Although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dose is required, special care should be exercised when initiating treatment in the elderly.

### **Use in Hepatic Impairment**

The pharmacokinetics of lercanidipine in patients with mild hepatic impairment are similar to those observed in the general population. However, there are no studies in patients with moderate hepatic impairment and dosage recommendations have not been established. Lercanidipine should therefore be used with caution in this patient group and careful monitoring undertaken during treatment, since the bioavailability and hypotensive effect may be increased. The use of lercanidipine in patients with moderate hepatic impairment should only be undertaken if the benefits are considered to outweigh the risks. Lercanidipine is contraindicated, in patients with severe hepatic disease.

### **Use in Renal Impairment**

Although the pharmacokinetics of lercanidipine in patients with mild to moderate renal impairment are similar to those observed in the general population, special care should be exercised when commencing treatment in such patients. The usual recommended dose of 10 mg daily may be tolerated; however, an increase to 20 mg daily should be approached with caution.

## INTERACTION WITH OTHER MEDICINES

Lercanidipine has been safely administered with diuretics and ACE inhibitors. It may also be administered safely with beta-blockers which are eliminated unchanged (such as atenolol).

### Inhibitors or Inducers of Cytochrome CYP3A4

Since the main metabolic pathway of lercanidipine involves the enzyme CYP3A4, drugs that inhibit or induce this enzyme have the potential to alter the plasma concentration of the compound.

Therefore, inhibitors of CYP3A4 (such as ketoconazole, itraconazole, erythromycin, ritonavir and fluoxetine) may increase the plasma concentration of lercanidipine, and such combinations should be used with caution.

When co-administered with CYP3A4 inducers, such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin, the antihypertensive effect of lercanidipine may be reduced and, therefore, blood pressure should be monitored when the co-administration is foreseen.

### CYP3A4 and CYP2D6 Substrates

The potential for *in vivo* inhibition of CYP3A4 by lercanidipine is negligible, as confirmed by an interaction study with midazolam in healthy volunteers. After repeated co-administration with lercanidipine, midazolam (a probe for CYP3A4 activity) was found to be essentially bioequivalent to the drug administered alone. However, unless specific data are available, caution should also be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4 which have a narrow therapeutic index, such as cyclosporin, and class III antiarrhythmic drugs (e.g. amiodarone and quinidine).

Co-administration of lercanidipine with cyclosporin resulted in a 3 fold increase in the plasma levels of lercanidipine and a 21% increase in the bioavailability of cyclosporin. However, when cyclosporin was administered 3 hours after lercanidipine, no increase in plasma levels was observed for lercanidipine, while the bioavailability of cyclosporine increased by 27%. Therefore, cyclosporin and lercanidipine should not be administered together.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of metoprolol, (a typical substrate of CYP2D6). Therefore, at therapeutic doses it is unlikely that lercanidipine will inhibit the biotransformation of drugs metabolized by CYP2D6.

These findings confirm that the inhibition of cytochrome P450 isoenzymes observed *in vitro* with lercanidipine is devoid of any clinical significance. *In vitro* experiments with human liver microsomes demonstrated that lercanidipine inhibits CYP3A4 and CYP2D6 (IC<sub>50</sub> of 2.6 µm and 0.8 µm, respectively). The IC<sub>50</sub> concentrations for CYP3A4 and CYP2D6 are 160 and 40 fold higher, respectively, than those reached at peak in the plasma after a 20 mg dose.

### Beta-Blockers

When lercanidipine was administered with metoprolol, a beta-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed, while that of lercanidipine was reduced by 50%. Therefore, when co-administered with metoprolol, it may be necessary to increase the dose of lercanidipine. It is anticipated that a similar effect may occur with propranolol.

### Cardiac Glycosides

Co-administration of lercanidipine in patients chronically treated with beta-methyl digoxin (a pro-drug of digoxin) showed no evidence of a pharmacokinetic interaction. However, patients on concomitant digoxin treatment should be closely monitored.

### Cimetidine

Concomitant administration of cimetidine 400 mg BD does not cause significant changes in the plasma levels of lercanidipine: AUC and C<sub>max</sub> were increased by a mean of 11%. However, at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

### Simvastatin

Co-administration of a 20 mg dose of lercanidipine with 40 mg simvastatin resulted in no increase in the bioavailability of lercanidipine, however a 56% increase was observed for simvastatin and a 28% increase for its active metabolite β-hydroxyacid. It is unlikely that these changes are clinically relevant. However, it is recommended that when required lercanidipine be administered in the morning and simvastatin in the evening.

Food

See previous section on pharmacokinetics.

The metabolism of dihydropyridines can be inhibited by grapefruit juice, leading to increased plasma concentration and hypotensive effect.

Alcohol should be avoided while taking lercanidipine since it may potentiate the effect of vasodilating antihypertensive drugs.

**ADVERSE EFFECTS**

Treatment with lercanidipine is generally well tolerated. In nine placebo-controlled clinical trials with a treatment duration lasting at least 4 weeks, 582 patients were initially treated with lercanidipine, and 292 patients received placebo. Most of the events reported in the studies were related to the vasodilatory effects of lercanidipine, and were classified mild-moderate in severity.

Table 1 lists, according to organ system, adverse events that were reported in placebo controlled trials in hypertensive patients with lercanidipine tablets at an incidence greater than or equal to 1% in at least one of the active treatment groups.

**Table 1:**

<b>ADVERSE EVENT</b>	<b>Lercanidipine 10 mg once daily (%)</b>	<b>Lercanidipine 20 mg once daily (titrated) (%)</b>	<b>Placebo (%)</b>
<b>CARDIOVASCULAR</b>			
Flushing	2.6	2.2	1.6
Palpitations/Tachycardia	1.5	1.1	0.3
<b>BODY AS A WHOLE</b>			
Peripheral oedema	1.0	1.1	0.9
<b>CENTRAL &amp; PERIPHERAL NERVOUS SYSTEM</b>			
Dizziness	1.0	0.0	0.6
Headache	4.4	4.3	2.5
<b>LIVER DISORDERS</b>			
GGT increased	0.0	1.1	0.3

More extensively, over 15,500 patients were treated with lercanidipine in clinical trials (including PMS studies) with doses from 2.5 mg daily up to 40 mg daily, and with treatment duration ranging from single dose up to more than 1 year. Adverse experiences which were not clearly drug related and which occurred in < 1% but ≥ 0.1% of patients are summarized according to organ system.

Cardiovascular:

Palpitations/tachycardia.

Central & Peripheral Nervous System:

Dizziness, vertigo.

Gastrointestinal:

Nausea, dyspepsia, abdominal pain, diarrhoea.

Psychiatric:

Somnolence.

General:

Flushing, asthenia (including fatigue and muscle weakness).

The following events have been rarely reported:

Cardiovascular:

Hypotension, orthostatic hypotension, periorbital oedema, anginal pain, myocardial infarction, cardiac failure.

Respiratory:

Dyspnoea.

Central & Peripheral Nervous System:

Migraine, paraesthesia, cramps legs.

Special Senses:

Taste alteration.

Gastrointestinal:

Vomiting, GI disorder NOS.

Liver & Biliary System:

GGT increased.

Genitourinary:

Polyuria, urinary frequency, impotence.

Musculoskeletal:

Myalgia.

Skin & Appendages:

Rash, pruritus, allergic dermatitis, hives, sweating increased.

Psychiatric:

Anxiety, insomnia.

Metabolic:

Hypercholesterolaemia.

General:

Chest pain, malaise.

Serious adverse events have been reported in clinical trials in less than 0.002% of the patients. The remaining adverse events have been reported as mild to moderate in intensity.

### **Laboratory Tests**

There were reports of isolated and reversible increases in serum levels of hepatic transaminases; no other clinically significant pattern of laboratory test abnormalities related to lercanidipine has been observed. Lercanidipine does not affect blood sugar or lipid levels.

### **DOSAGE AND ADMINISTRATION**

The recommended dose is 10 mg once daily, at least 15 minutes before a meal. The dose may be increased to 20 mg once daily depending on the individual response. Dose titration should be gradual, as it may take about 2 weeks for the maximal antihypertensive effect to be apparent. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. Since it is unlikely that increasing the dose beyond 20 mg will further improve the efficacy, and may be associated with side effects, doses above 20 mg are not recommended. Some individuals not adequately controlled on a single antihypertensive agent may benefit from the addition of lercanidipine at the same doses used in monotherapy to the existing regimen with a beta-blocker, a diuretic or an ACE-inhibitor.

### **Use in Elderly, Children, Hepatic and Renal Impairment**

See PRECAUTIONS.

## **OVERDOSAGE**

There is limited experience with lercanidipine overdose. As with other dihydropyridines, overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular and respiratory monitoring will be required, and supportive treatment may be necessary. Since lercanidipine is highly lipophilic, dialysis is unlikely to be effective.

**For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).**

## **PRESENTATION AND STORAGE CONDITIONS**

APO-Lercanidipine tablets are intended for oral administration.

Each tablet contains 10 mg or 20 mg lercanidipine hydrochloride, as the active ingredient.

**10 mg tablets:** Yellow coloured, film coated, round shaped, biconvex tablets, engraved 'APO' on one side and score line on the other side.

Blister packs (PVC/PE/PVDC/Aluminium) of 14, 28 and 30 tablets: AUST R 163768.  
Bottles (HDPE) of 30, 100 and 500 tablets: AUST R 163765.

**20 mg tablets:** Pink coloured, film coated, round shaped, biconvex tablets, engraved 'APO' on one side and score line on the other side.

Blister packs (PVC/PE/PVDC/Aluminium) of 14, 28 and 30 tablets: AUST R 163769.  
Bottles (HDPE) of 30, 100 and 500 tablets: AUST R 163762.

Not all pack sizes or pack types may be available.

### **Storage**

Store below 30°C.

## **NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
16 Giffnock Avenue Macquarie Park NSW 2113  
Australia

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## **POISONS SCHEDULE OF THE MEDICINE**

S4 : Prescription Only Medicine.

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 5 August 2010**

Date of most recent amendment:: 14 July 2014