Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lercanidipine Teva Pharma 20 mg Film-coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 20 mg of lercanidipine hydrochloride, which is equivalent to 18.8 mg of lercanidipine.

Excipients
One tablet contains 60 mg of lactose monohydrate (equivalent to 57 mg of lactose anhydrous) and 0.711 mg of allura red AC aluminium lake (E129).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Light pink to pink, round convex film−coated tablet debossed with the number "20" on one side and scored on the other

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lercanidipine is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Method of administration

Oral route
The tablet should be swallowed with sufficient liquid (*e.g.* a glass of water).

Dosage

The recommended dosage is 10 mg orally once a day at least 15 minutes before meals; the dose may be increased to 20 mg depending on the individual patient's response.

Dose titration should be gradual, because it may take about 2 weeks before the maximal antihypertensive effect is apparent.

Some individuals, not adequately controlled on a single antihypertensive agent, may benefit from the addition of lercanidipine to therapy with a beta−adrenoceptor blocking agent (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin-converting enzyme inhibitor (captopril or enalapril).

Since the dose-response curve is steep with a plateau at doses between 20-30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

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

Use in children and adolescents
Since there is no clinical experience in patients under the age of 18 years, use in children is not currently recommended.

Use in renal or hepatic dysfunction
Special care should be exercised when treatment is commenced in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule may be tolerated by these subgroups, an increase in dose to 20 mg daily must be approached with caution. The antihypertensive effect may be enhanced in patients with hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine should not be used in patients with severe hepatic impairment or in patients with severe renal impairment (glomerular filtration rate < 30 ml/min) (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance, to any dihydropyridine or to any of the excipients
- Pregnancy and lactation
- Women of child−bearing potential unless effective contraception is used
- Left ventricular outflow tract obstruction
- Untreated congestive cardiac failure
- Unstable angina pectoris
- Severe renal or hepatic impairment
- Within 1 month of a myocardial infarction
- Co-administration with
  - strong inhibitors of CYP3A4 (see section 4.5)
  - ciclosporin (see section 4.5)
  - grapefruit juice (see section 4.5)

4.4 Special warnings and precautions for use

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not *in situ*). Although haemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with left ventricular dysfunction. 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 is required in such patients.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre−existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see section 4.8).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive medicinal products (see section 4.5).

Inducers of CYP3A4 like anticonvulsants (*e.g.* phenytoin, carbamazepine) and rifampicin may reduce lercanidipine's plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take it.

This medicinal product contains allura red AC aluminium lake (E129) and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Lercanidipine is known to be metabolised by the CYP3A4 enzyme and, therefore, inhibitors and inducers of CYP3A4 administered concurrently may interact with the metabolism and elimination of lercanidipine.

Co-prescription of lercanidipine with inhibitors of CYP3A4 (*e.g.* ketoconazole, itraconazole) should be avoided (see section 4.3).

An interaction study with a strong CYP3A4 inhibitor, ketoconazole, has shown a considerable increase in plasma levels of lercanidipine (a 15−fold increase of the area-under-the-curve (AUC) and an 8−fold increase of the peak plasma concentration (C_{max}) for the eutomer *S*-lercanidipine).

Ciclosporin and lercanidipine should not be administered together (see section 4.3). Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when ciclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of ciclosporin increased by 27%. However, the co−administration of lercanidipine with ciclosporin has caused a 3−fold increase of the plasma levels of lercanidipine and a 21% increase of the ciclosporin AUC.

Lercanidipine should not be taken with grapefruit juice (see section 4.3). Dihydropyridines including lercanidipine are sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in their systemic availability and increased hypotensive effect.

When concomitantly administered at a dose of 20 mg with midazolam *per os* to elderly volunteers, lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased (the time to peak plasma concentration (t_{max}) was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

Caution should be exercised when lercanidipine is co−prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic agents such as amiodarone, quinidine.

Co−administration of lercanidipine with CYP3A4 inducers like anticonvulsants (*e.g.* phenytoin, carbamazepine) and rifampicin should be approached with caution since the antihypertensive effect may be reduced and blood pressure should be monitored more frequently than usual.

When lercanidipine was co−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%. This effect may be due to the reduction in the hepatic blood flow caused by beta−blockers and may therefore occur with other medicinal products of this class. Consequently, lercanidipine may be safely administered with beta−blocking agents, but dose adjustment may be required.

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± standard deviation), has shown no clinically relevant modification of the pharmacokinetics of lercanidipine.

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Co−administration of 20 mg lercanidipine in patients chronically treated with beta-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin C_{max}, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

When a dose of 20 mg of lercanidipine was repeatedly co−administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, while simvastatin's AUC increased by 56% and that of its active metabolite beta−hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such medicinal products.

The co−administration of 20 mg lercanidipine to healthy volunteers given fasted did not alter the pharmacokinetics of warfarin.

Lercanidipine has been safely administered with diuretics and angiotensin−converting enzyme inhibitors.

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive agents (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by channel blockers. In cases where repeated in vitro fertilisation is unsuccessful and where another explanation cannot be found, the possibility of calcium channel blockers as the cause should be considered.

Pregnancy

Animal studies with lercanidipine have not shown teratogenic effects, but these have been observed with other dihydropyridine compounds (see section 5.3).

No clinical data on exposed pregnancies are available for lercanidipine, therefore it should not be used during pregnancy or in women planning to become pregnant.

Lactation

The excretion of lercanidipine in human milk is unknown. Consequently, it should not be used during lactation.

4.7 Effects on ability to drive and use machines

Lercanidipine has no or negligible influence on the ability to drive and use machines. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.

4.8 Undesirable effects

About 1.8% of treated patients experienced adverse reactions.

The following undesirable effects have been reported in clinical studies and in the post−marketing phase.

Assessment of frequencies:
Very common: ≥1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known (cannot be estimated from the available data)

As shown in the table, the most commonly occurring adverse drug reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

System organ class		Adverse drug reactions
Immune system disorders	Very rare	Hypersensitivity
Psychiatric disorders	Rare	Somnolence
Nervous system disorders	Uncommon	Headache, dizziness
	Not known	An extrapyramidal syndrome has been reported with some calcium antagonists.
Cardiac disorders	Uncommon	Tachycardia, palpitations, peripheral oedema
	Rare	Angina pectoris
	Very rare	Chest pain, myocardial infarction, hypotension
	Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely, patients with pre−existing angina pectoris may experience increased frequency, duration or severity of these attacks.	
Vascular disorders	Uncommon	Flushing
	Very rare	Syncope
Gastrointestinal disorders	Rare	Dyspepsia, nausea, diarrhoea, abdominal pain, vomiting
	Very rare	Gingival hypertrophy
Skin and subcutaneous tissue disorders	Rare	Rash
Musculoskeletal and connective tissue disorders	Rare	Myalgia
Renal and urinary disorders	Rare	Polyuria
	Very rare	Urinary frequency
General disorders and administration site conditions	Uncommon	Peripheral oedema
	Rare	Asthenia, fatigue

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely: gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.

Lercanidipine does not appear to adversely influence blood sugar or serum lipid levels.

4.9 Overdose

Symptoms

Overdose might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia.

In post−marketing experience, three cases of overdose have been reported. The first patient developed sleepiness. The second patient developed cardiogenic shock with severe myocardial ischaemia and mild renal failure. The third patient showed vomiting and hypotension. All patients recovered resolved without sequelae.

Treatment

In the above−mentioned cases, treatment consisted respectively in gastric lavage; high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders; activated charchoal, laxatives and intravenous dopamine. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support can be helpful, with intravenous atropine to counteract the bradycardia.

In view of the prolonged pharmacological action of lercanidipine, the cardiovascular status of patients who have taken an overdose must be monitored for at least 24 hours. There is no information on the value of dialysis. Since the substance is highly lipophilic, it is very unlikely that plasma levels will be indicative of the duration of the risk phase. Dialysis may not be effective.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects
ATC code: C08C A13

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance. Despite its short pharmacokinetic plasma half−life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.

Since the vasodilatation induced by lercanidipine 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 its *S*-enantiomer.

5.2 Pharmacokinetic properties

Lercanidipine is completely absorbed after oral administration of 10-20 mg lercanidipine hydrochloride and peak plasma levels, 3.30 ng/ml ± 2.09 standard deviation and 7.66 ng/ml ± 5.90 standard deviation respectively, occur about 1.5-3 hours after dosing.

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2−fold higher for the *S*−enantiomer and the elimination half-lives of the two enantiomers are essentially the same. No *in vivo* interconversion of enantiomers is observed.

Due to the high first−pass metabolism, the absolute bioavailability of lercanidipine orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.

Oral availability of lercanidipine increases 4−fold when it is ingested up to 2 hours after a high−fat meal. Accordingly, lercanidipine should be taken before meals.

Distribution from plasma to tissues and organs is rapid and extensive.

The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Lercanidipine is extensively metabolised by CYP3A4; no parent substance is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

In vitro experiments with human liver microsomes have demonstrated that lercanidipine shows some degree of inhibition of CYP3A4 and CYP2D6, at concentrations 160- and 40−fold, respectively, higher than those reached at peak in the plasma after the dose of 20 mg.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, inhibition of biotransformation of substances metabolised by CYP3A4 and CYP2D6 by lercanidipine is not expected at therapeutic doses.

Elimination occurs essentially by biotransformation.

A mean terminal elimination half life of 8-10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Oral administration leads to plasma levels of lercanidipine not directly proportional to dosage (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, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of lercanidipine was shown to be similar to that observed in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the substance. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since it is normally metabolised extensively in the liver.

5.3 Preclinical safety data

Safety pharmacological studies in animals have shown no effects on the autonomic nervous system, the central nervous system or on gastrointestinal function at antihypertensive doses.

The relevant effects which have been observed in long−term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of calcium antagonists, predominantly reflecting exaggerated pharmacodynamic activity.

Lercanidipine was not genotoxic and showed no evidence of carcinogenic hazard.

Fertility and general reproductive performance in rats were unaffected by treatment with lercanidipine.
There was no evidence of any teratogenic effect in rats and rabbits; however, in rats, lercanidipine at high dose levels induced pre- and post−implantation losses and delay in fetal development.

Lercanidipine hydrochloride, when administered at high dose (12 mg/kg/day) during labour, induced dystocia.

The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:	Lactose monohydrate
	Sodium starch glycolate (potato)
	Microcrystalline cellulose
	Povidone
	Magnesium stearate
Film-coating:	Opadry 03F34650 pink containing:
	hypromellose (E464)
	titanium dioxide (E171)
	allura red AC aluminium lake (E129)
	macrogol 6000
	talc
	indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blisters: 3 years
Bottles: 2 years
Bottles (after first opening container): 30 days

6.4 Special precautions for storage

Blisters
Store in the original package in order to protect from light.

Bottles
Store in the original package in order to protect from light.

Bottles (after first opening container)
Store in the original package in order to protect from light

6.5 Nature and contents of container

Blisters
White opaque PVC/PVdC – aluminium blisters
15, 28, 30, 50, 56, 60, 90, 98, 100 tablets and Hospital pack: 50x1 tablets -Calendar packs of 28 tablets.

Bottles
40 ml white HDPE bottle with 33 mm child-resistant white polypropylene closure and 1 g silica gel desiccant
30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/183/002

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