PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ZANIDIP 10 mg film-coated tablets

ZANIDIP 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZANIDIP 10: Each film-coated tablet contains lercanidipine hydrochloride 10 mg equivalent to 9,4 mg lercanidipine.

Contains sugar (lactose monohydrate): 30 mg per film-coated tablet.

ZANIDIP 20: Each film-coated tablet contains lercanidipine hydrochloride 20 mg equivalent to 18,8 mg lercanidipine.

Contains sugar (lactose monohydrate): 60 mg per film-coated tablet.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

ZANIDIP 10: Yellow, circular, biconvex film-coated tablets, scored on one side.

ZANIDIP 20: Pink, circular, biconvex film-coated tablets, scored on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZANIDIP is indicated for the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

The recommended starting dosage is 10 mg orally once a day at least 15 minutes before a meal. In patients not responding adequately, 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.

Elderly patients

Although 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.

Paediatric population

The safety and efficacy of ZANIDIP in children aged up to 18 years have not been established.

No data are available.

Patients with renal or hepatic impairment

Special care should be exercised when treatment is commenced in patients with renal or hepatic dysfunction.

Although the recommended dosage schedule may be tolerated by these subgroups, an increase in dosage 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.

ZANIDIP contraindicated for use in patients with severe hepatic dysfunction or in patients with severe renal dysfunction GFR < 30 ml/min) including patients undergoing dialysis (see sections 4.3 and 4.4).

Method of administration

ZANIDIP should not be administered with grapefruit juice (see section 4.3 and 4.5).

4.3 Contraindications

- Hypersensitivity to lercanidipine or to any of the excipients (see section 6.1).
- Women of childbearing potential unless effective contraception is used.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris, or recent (within 1 month) of a myocardial infarction.
- Severe hepatic impairment.
- Severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis.
- Since there is no clinical experience in patients under the age of 18 years, use in children is not recommended.
- ZANIDIP is contraindicated during pregnancy and lactation (see section 4.6).
- Co-administration with:
  - inhibitors of CYP3A4 (see section 4.5),
  - ciclosporin (see section 4.5).
  - grapefruit or grapefruit juice (see section 4.5)

4.4 Special warnings and precautions for use

Sick sinus syndrome

Lercanidipine should be administered with caution in patients with sick sinus syndrome (without a pacemaker).

Left ventricular dysfunction

Although haemodynamic controlled studies revealed no impairment of ventricular function, care is required in patients with moderate to severe left ventricular dysfunction.

Ischaemic heart disease

It has been suggested that some short-acting dihydropyridine may be associated with increased cardiovascular risk in patients with ischemic heart disease. Although lercanidipine is a long-acting dihydropyridine, 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).

Use in renal or hepatic impairment

Special care should be exercised when treatment is commenced in patients with mild to moderate renal impairment. Although the usual~~ly~~ recommended dose of 10 mg daily may be tolerated, an increase to 20 mg daily should be approached with caution.

The antihypertensive effect may be enhanced in patients with moderate hepatic impairment and consequently an adjustment of the dosage should be considered.

Lercanidipine is contraindicated in patients with severe hepatic impairment or renal impairment (GFR <30 ml/min), including patients undergoing haemodialysis (see section 4.2 and 4.3).

Peritoneal dialysis

Lercanidipine has been associated with the development of cloudy peritoneal effluent in patients on peritoneal dialysis. The turbidity is due to an increased triglyceride concentration in the peritoneal effluent. Whilst the mechanism is unknown, the turbidity tends to resolve soon after withdrawal of lercanidipine. This is an important association to recognise as cloudy peritoneal effluent can be mistaken for infective peritonitis with consequential unnecessary hospitalisation and empiric antibiotic administration.

Inducers of CYP3A4

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

Alcohol

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

Lactose

Contains lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZANIDIP.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium

ZANIDIP contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Peadiatric population

The safety and efficacy of lercanidipine have not been demonstrated in children.

4.5 Interaction with other medicines and other forms of interaction

Contraindications of concomitant use

Inhibitors of CYP3A4

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

elimination of lercanidipine. 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 AUC and an 8-fold increase of the C_{max} for the eutomer S-lercanidipine).

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

Ciclosporin

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.

Ciclosporin and lercanidipine should not be administered together (see section 4.3).

Grapefruit or grapefruit juice

As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit or grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see section 4.3).

Concomitant use not recommended

Inducers of CYP3A4

Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, phenobarbital, 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 (see section 4.4).

Alcohol

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

Precautions including dose adjustments

Substrates of CYP3A4

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

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine absorption was increased (by approximately 40 %) and the rate of absorption was decreased (t_{max} was delayed from 1,75 to 3 hours). Midazolam concentrations were not modified.

Metoprolol

When lercanidipine was co-administered with metoprolol, a β-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 β-blockers and may therefore occur with other medicines of this class. Consequently, lercanidipine may be safely administered with β-adrenoceptor blocking medicines, but dose adjustment may be required.

Digoxin

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

Concomitant use with other medicines

Fluoxetine

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

Cimetidine

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.

Simvastatin

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 AUC increased by 56 % and that of its active metabolite β-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 medicine.

Warfarin

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

Diuretics and ACE inhibitors

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Other medicines affecting blood pressure

As for all antihypertensive medicines, an increased hypotensive effects may be observed when lercanidipine is administered with other medicines affecting blood pressure, such as alpha-blockers for the treatment of urinary symptoms, tricyclic antidepressants, neuroleptics. On the contrary, a reduction of the hypotensive effect may be observed with a concomitant use with corticosteroids.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of lercanidipine in pregnant women. Studies in animals have not shown teratogenic effects (see section 5.3), but these have been observed with other dihydropyridine compounds. Lercanidipine is not recommended during pregnancy and in women of childbearing-potential not using contraception.

Lactation

It is unknown whether lercanidipine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lercanidipine should not be used during lactation.

Fertility

No clinical data are available with lercanidipine. 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.

4.7 Effects on ability to drive and use machines

ZANIDIP has minor 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

a. Summary of the safety profile

The safety of lercanidipine at a dose of 10 - 20 mg once daily has been evaluated in double-blind, placebo-controlled clinical trials (with 1 200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long term clinical trials on a total of 3 676 hypertensive patients receiving lercanidipine.

The most commonly reported adverse reactions in clinical trials and in the post-marketing experience are: peripheral oedema, headache, flushing, tachycardia and palpitations.

b. Tabulated summary of adverse reactions

In the table below, adverse reactions reported in clinical trials and in the worldwide post marketing experience for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: 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). Within each frequency grouping the observed adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Immune system disorders	Rare	Hypersensitivity
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Somnolence, syncope
Cardiac disorders	Common	Tachycardia, palpitations
	Rare	Angina pectoris
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
Gastrointestinal disorders	Uncommon	Upper abdominal pain, dyspepsia, nausea
	Rare	Diarrhoea, vomiting
	Not known	Gingival hypertrophy[1], peritoneal cloudy effluent[1]
Hepato-biliary disorders	Not known	Increased serum transaminases
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritis
	Rare	Urticaria
	Not known	Angioedema[1]
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
Renal and urinary disorders	Uncommon	Polyuria
	Rare	Pollakiuria

System organ class	Frequency	Adverse reactions
General disorders and administration site conditions	Common	Peripheral oedema
	Uncommon	Asthenia, fatigue
	Rare	Chest pain

[1] adverse reactions from spontaneous reporting in the worldwide post-marketing experience

c. Description of selected adverse reactions

In placebo controlled clinical trials the incidence of peripheral oedema was 0,9 % with lercanidipine 10-20 mg and 0,83 % with placebo. This frequency reached 2 % in the overall study population including long term clinical trials.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via: to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. You can also report side effects to Acino Pharma (Pty) Ltd via email on: drugsafety_ZA@acino.swiss.

4.9 Overdose

In the post-marketing experience of lercanidipine, some cases of overdose have been reported ranging from 30 - 40 mg up to 800 mg, including reports of suicide attempt.

Symptoms

As with other dihydropyridines, lercanidipine overdosage results in excessive peripheral vasodilation with marked hypotension and reflex tachycardia. However, at very high doses, the peripheral selectivity may be lost, causing bradycardia and a negative inotropic effect. The most common ADRs associated to cases of overdose have been hypotension, dizziness, headache and palpitations.

Treatment

Clinically significant hypotension requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output. In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of the patient is monitored for 24 hours at least. Since the product has a high protein binding, dialysis is not likely to be effective. Patients in whom a moderate to severe intoxication is anticipated should be observed in a high-care setting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1 Vasodilators, hypotensives.

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects – Dihydropyridine derivatives

ATC code: C08CA13.

Mechanism of action

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 peripheral resistance.

Pharmacodynamic effects

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 vasodilation 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.

Clinical efficacy and safety

The clinical efficacy and safety of lercanidipine at a dose of 10-20 mg once daily has been evaluated in double-blind, placebo-controlled clinical trials (with 1 200 patients receiving lercanidipine and 603 patients receiving placebo) and in active-controlled and uncontrolled long term clinical trials on a total of 3 676 hypertensive patients.

Most clinical trials have been conducted in patients with mild to moderate essential hypertension (including elderly and diabetic patients), receiving lercanidipine alone or in combination with ACE-Is, diuretics or beta-blockers.

In addition to the clinical studies conducted to support the therapeutic indications, a further small uncontrolled but randomised study of patients with severe hypertension (mean + SD diastolic blood pressure of 114,5 + 3,7 mmHg) showed that blood pressure was normalised in 40 % of the 25 patients on 20 mg once daily dose and in 56 % of 25 patients on 10 mg twice daily doses of ZANIDIP. In a double-blind, randomised, controlled study versus placebo in patients with isolated systolic hypertension ZANIDIP was efficacious in lowering systolic blood pressure from mean initial values of 172,6 + 5,6 mmHg to 140,2 + 8,7 mmHg.

Paediatric population

No clinical trial has been performed in the paediatric population.

5.2 Pharmacokinetic properties

Absorption

Lercanidipine is completely absorbed after 10 - 20 mg oral administration and peak plasma levels, 3,30 ng/ml + 2,09 s.d. and 7,66 ng/ml + 5,90 s.d. 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 ZANIDIP 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 ZANIDIP is ingested up to 2 hours after a high fat meal. Accordingly, ZANIDIP should be taken before meals.

Distribution

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 medicine may be increased.

Biotransformation

Lercanidipine is extensively metabolised by CYP3A4; no parent drug 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 drugs metabolised by CYP3A4 and CYP2D6 by ZANIDIP is not expected at therapeutic doses.

Elimination

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.

Linearity/non-linearity

Oral administration of lercanidipine 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.

Additional information on special populations

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 medicine. In patients with severe hepatic impairment, the systemic bioavailability of

lercanidipine is likely to be increased since the medicine is normally metabolised extensively in the liver.

5.3 Preclinical safety data

Non–clinical data reveal no special hazard for human based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

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 Ca- 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 foetal 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

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycolate

Povidone K30

Magnesium stearate

Film-coating

Hypromellose

Talc

Titanium dioxide (E171)

Macrogol 6000

Ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light. Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Aluminium / opaque PVC blisters.

Packs of 14, 28, 35, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

8 REGISTRATION NUMBERS

ZANIDIP 10: 33/7.1/0113

ZANIDIP 20: A40/7.1/0106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Zanidip 10: 2 April 2004

Zanidip 20: 1 December 2006

10 DATE OF REVISION OF THE TEXT

02 April 2025

Registration No.:
Namibia NS3
Zanidip 10: 06/7.1/0169
Zanidip 20: 06/7.1/0001