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SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ZANIDIP 10 tablets

ZANIDIP 20 tablets

COMPOSITION

ZANIDIP 10: Each tablet contains lercanidipine hydrochloride 10 mg.

ZANIDIP 20: Each tablet contains lercanidipine hydrochloride 20 mg.

Excipients: ferric oxide (E172), hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, titanium dioxide (E171)

Contains sugar: lactose

CATEGORY AND CLASS

A 7.1 Vasodilators, hypotensives.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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. 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.

The antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Pharmacokinetic properties

Lercanidipine is completely absorbed after 10 to 20 mg oral administration and peak plasma levels of 3,30 ng/ml ± 2,09 s.d. and 7,66 ng/ml ± 5,90 s.d. respectively, occur about 3 to 4 hours after dosing.

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.

The absolute bioavailability or orally administered lercanidipine is relatively low as a consequence of high first pass metabolism.

The pharmacokinetic half-life is 3 to 5 hours but the therapeutic activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Lercanidipine is extensively metabolised by CYP 3A4; no parent drug is found in the urine or faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

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 the plasma concentration-time curves in the

ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

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.

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

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 drug. In patients with severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolised extensively in the liver.

INDICATIONS

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

CONTRAINDICATIONS

- Hypersensitivity to **ZANIDIP**, dihydropyridine or any other ingredient of the preparation.
- Women of childbearing potential unless effective contraception is used.
- Patients with left ventricular outflow tract obstruction, untreated congestive cardiac failure, unstable angina pectoris, severe renal or hepatic dysfunctions or within 1 month of a myocardial infarction.

- 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 **HUMAN REPRODUCTION**).
- **ZANIDIP should not be taken with grapefruit juice.**
- Co-administration of **ZANIDIP** with inhibitors of CYP3A4 e.g. ketoconazole, itraconazole, erythromycin, ritonavir, troleandomycin and fluoxetine are contraindicated.
- Cyclosporine and **ZANIDIP** should not be administered together.

WARNINGS AND SPECIAL PRECAUTIONS

Special care should be exercised when **ZANIDIP** is used in patients with sick sinus syndrome (if a pacemaker is not in situ) and in patients with LV outflow tract obstruction. Although haemodynamic controlled studies revealed no impairment of ventricular function, care is required in patients with moderate to severe LV dysfunction. Short-acting dihydropyridine may be associated with increased cardiovascular risk in patients with ischemic heart disease. Although **ZANIDIP** is a long-acting dihydropyridine, caution is required in these 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.

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 (see **DOSAGE AND DIRECTIONS FOR USE**).

ZANIDIP is not recommended for use in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30 ml/min).

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.

INTERACTIONS:

Caution should be exercised when combining **ZANIDIP** with beta-adrenergic blocking ~~drugs~~ medicines which are metabolised in the liver (such as propranolol and metoprolol) as there is a risk of increased hypotensive effect.

Patients on concomitant digoxin therapy should be closely monitored clinically for signs of digoxin toxicity.

Caution is required if cimetidine is administered concomitantly.

The main metabolic pathway involves the enzyme CYP3A4. Caution is recommended when **ZANIDIP** is co-prescribed with:

- Inducers of CYP3A4 e.g. phenytoin, carbamazepine and rifampicin, as the antihypertensive effect may be reduced, and blood pressure should be monitored more frequently than usual.
- Other substrates of CYP3A4 e.g. terfenadine, astemizole, Class III antiarrhythmic medicines such as amiodarone and quinidine, some benzodiazepines such as diazepam and midazolam, propranolol and metoprolol.

- Inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, fluoxetine) should be avoided (see **CONTRAINDICATIONS**).

Co-administration of **ZANIDIP** with anticonvulsants should be approached with caution. The antihypertensive effect of **ZANIDIP** may be reduced and blood pressure should be monitored more frequently than normal.

Cyclosporin and **ZANIDIP** should not be administered together (see **CONTRAINDICATIONS**). Increased plasma levels of both lercanidipine and cyclosporin have been observed following concomitant administration.

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's absorption was increased and the rate of absorption was decreased). Midazolam concentrations were not modified.

ZANIDIP appears to be particularly sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in the systemic availability of up to 8-fold thereof.

Alcohol should be avoided since it may potentiate the effects of **ZANIDIP**.

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **ZANIDIP**

HUMAN REPRODUCTION

There is no clinical experience with **ZANIDIP** in pregnancy and lactation; **ZANIDIP** should therefore not be administered during pregnancy or to woman with child-bearing potential unless effective contraception is used.

Because of high lipophilicity of **ZANIDIP**, distribution in milk may be expected. **ZANIDIP** should therefore not be administered to nursing mothers.

DOSAGE AND DIRECTIONS FOR USE

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.

Use in the elderly

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.

Use in renal or hepatic dysfunction

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.

ZANIDIP is not recommended for use in patients with severe hepatic dysfunction or in patients with severe renal dysfunction (creatinine clearance < 10 ml/min).

SIDE EFFECTS

MedDRA System Organ Class	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000);**	**Very rare (<1/10,000)**
Immune system disorders			hypersensitivity
Nervous system disorders	dizziness; headache;	somnolence	syncope; mental depression
Cardiac disorders	tachycardia; palpitations	angina pectoris	hypotension, precordial pain, myocardial infarction, chest pain
Vascular disorders	flushing, peripheral oedema		
Gastrointestinal disorders		abdominal pain; diarrhoea; dyspepsia; nausea; vomiting	gingival hyperplasia
Skin and subcutaneous tissue disorders		rash	
Musculoskeletal and connective tissue disorders		myalgia	

MedDRA System Organ Class	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000);	Very rare (<1/10,000)
Renal and urinary disorders		polyuria	increased micturition frequency
Hepatobiliary disorders			isolated and reversible increases in serum levels of hepatic transaminases
General disorders and administration site conditions		asthenia; fatigue	
Eye disorders			eye pain

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and reflex tachycardia. In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support could be helpful, with intravenous atropine for bradycardia.

In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of patients who take an overdose is monitored for at least 24 hours.

Treatment is symptomatic and supportive.

IDENTIFICATION

ZANIDIP 10: Yellow, round scored film-coated tablets.

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

PRESENTATION

ZANIDIP 10: Aluminium / opaque PVC blister packs of 14, 28, 35, 50 and 100 tablets.

ZANIDIP 20: Aluminium / opaque PVC blister packs of 28 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 ºC.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

ZANIDIP 10: 33/7.1/0113

ZANIDIP 20: A40/7.1/0106

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Litha Pharma (Pty) Ltd

106 16th Road

Midrand

DATE OF PUBLICATION OF THE PROFFESIONAL INFORMATION

Date of registration: 2 April 2004 (10 mg); 1 December 2006 (20 mg)

Date of most recent amendment: 15 May 2017