

## PACKAGE INSERT

### **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)

### **PHARMACOLOGICAL CLASSIFICATION:**

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  $3,30 \text{ ng/ml} \pm 2,09 \text{ s.d.}$  and  $7,66 \text{ ng/ml} \pm 5,90 \text{ s.d.}$  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 of 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 contra-indicated during pregnancy and lactation (see **PREGNANCY AND LACTATION**).

**ZANIDIP should not be taken with grapefruit juice.**

Co-administration of **ZANIDIP** with inhibitors of CYP3A4 e.g. ketoconazole, itraconazole, erythromycin and fluoxetine is 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.

### **INTERACTIONS:**

Caution should be exercised when combining **ZANIDIP** with beta-adrenergic blocking drugs 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 CYP 3A4. Caution is recommended when **ZANIDIP** is co-prescribed with:

- Inducers of CYP 3A4 e.g. phenytoin, carbamazepine and rifampicin; and/or;
- Other substrates of CYP 3A4 e.g. terfenadine, astemizole, Class III antiarrhythmic drugs such as amiodarone and quinidine, some benzodiazepines such as diazepam and midazolam, propranolol and metoprolol.

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.

**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**.

#### **PREGNANCY AND LACTATION:**

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:**

The side-effect frequencies are listed according to the following convention:

Common ( $>1/100 \leq 1/10$ );

Uncommon ( $>1/1\ 000 \leq 1/100$ );

Rare ( $>1/10\ 000 \leq 1/1\ 000$ )

### **Nervous system disorders:**

Common: Dizziness, headache

Uncommon: Fatigue, somnolence

Mental depression has been reported with **ZANIDIP**.

**Eye disorders:**

Eye pain has been reported with **ZANIDIP**.

**Cardiac and vascular disorders:**

Common: Flushing, tachycardia, peripheral oedema

Adverse events that have been reported with **ZANIDIP** are hypotension and palpitations, precordial pain, angina pectoris and myocardial infarction. Patients with pre-existing anginal pectoris have reported an increase in frequency, duration or severity of these attacks.

**Gastrointestinal disorders:**

Uncommon: Nausea, dyspepsia, abdominal pain, diarrhoea, vomiting

**Hepato-biliary disorders:**

Isolated and reversible increases in serum levels of hepatic transaminases have been reported.

**Skin and subcutaneous disorders:**

Uncommon: Rash

Gingival hyperplasia has been reported with **ZANIDIP**.

**Musculoskeletal, connective tissue and bone disorders:**

Uncommon: Myalgia

**Renal and urinary disorders:**

Rare: Polyuria.

Increased micturition frequency has been reported with **ZANIDIP**.

**General disorders:**

Common: Asthenia

### **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 °C.

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

KEEP OUT OF REACH OF CHILDREN.



**REGISTRATION NUMBER:**

**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

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Midrand

**DATE OF PUBLICATION OF THE PACKAGE INSERT:**

Original date of registration and approved package insert: 1 December 2006