PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZERCAP® 10, film-coated tablets

ZERCAP® 20, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg lercanidipine hydrochloride equivalent to 9,4 mg lercanidipine, or 20 mg lercanidipine hydrochloride equivalent to 18,8 mg lercanidipine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ZERCAP 10 are yellow, round, biconvex, film-coated tablets with a breakline on one side and plain on the other side.

ZERCAP 20 are pink, round, biconvex, film-coated tablets with a breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended starting dose 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.

Special populations

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.

ZERCAP is not recommended for use in patients with severe hepatic dysfunction or in patients with severe renal dysfunction (creatinine clearance < 10 mL/min); see sections 4.3 and 4.4.

Paediatric population

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

Method of administration

ZERCAP should be taken orally, at least 15 minutes before a meal.
The score line is only to facilitate breaking if required for ease of swallowing, and not to divide the tablet into equal doses.

4.3 Contraindications

- Hypersensitivity to lercanidipine, dihydropyridine or any other ingredient of ZERCAP (see section 6.1).
- Patients with left ventricular outflow tract obstruction, untreated congestive cardiac failure, unstable angina pectoris or within 1 month of a myocardial infarction.
- Severe renal or hepatic dysfunction.
- **ZERCAP should not be taken with grapefruit juice (see section 4.5)**
- Co-administration with:
    - inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin and fluoxetine - see section 4.5)
    - ciclosporin (see section 4.5)
- Pregnancy and lactation (see section 4.6).

- Women of child-bearing potential unless effective contraception is used.
- Since there is no clinical experience in patients under the age of 18 years, use in children is not recommended.

4.4 Special warnings and precautions for use

Sick sinus syndrome

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not *in situ*) and in patients with left ventricular (LV) outflow tract obstruction.

Left ventricular dysfunction

Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with left ventricular dysfunction.

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 is required in such patients. Some dihydropyridines may lead to precordial pain or angina pectoris. 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 taken when treatment is started in patients with mild to moderate renal impairment. Although the usual recommended dose of

10 mg daily may be tolerated, an increase to 20 mg daily must 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.

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

Peritoneal dialysis

Lercanidipine, contained in ZERCAP, 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. While the mechanism is unknown, the turbidity tends to resolve soon after withdrawal of ZERCAP. 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 the plasma levels of lercanidipine and therefore the efficacy of ZERCAP may be less than expected (see section 4.5).

Alcohol

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

Paediatric population

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

4.5 Interactions with other medicines and other forms of interaction

Contraindications of concomitant use

Inhibitors of CYP3A4

Lercanidipine appears to be particularly sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability of up to 8-fold thereof. ZERCAP may not be taken with grapefruit juice (see section 4.3).

Lercanidipine is 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 ZERCAP with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) is contraindicated (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 ZERCAP with ciclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21 % increase of the ciclosporin AUC.

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

Concomitant use not recommended

Inducers of CYP3A4

Co-administration of ZERCAP with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine) and rifampicin should be approached with caution. The antihypertensive effect of ZERCAP 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 adjustment

Substrates of CYP3A4

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

Benzodiazepines

Caution is required if benzodiazepines like diazepam, midazolam are co-prescribed with ZERCAP.

When concomitantly administered at a dose of 20 mg with midazolam, in elderly volunteers, absorption of lercanidipine was increased (by approximately 40 %) and the rate of absorption decreased. The midazolam concentrations were not modified.

Metoprolol

When lercanidipine (contained in ZERCAP) 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, ZERCAP may be safely administered with β-adrenoceptor blocking medicines, but dose adjustment may be required.

Digoxin

Co-administration of 20 mg lercanidipine (contained in ZERCAP) 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

No clinically relevant modification of the pharmacokinetics of lercanidipine is expected with concomitant administration of ZERCAP and fluoxetine.

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

No interaction is expected when ZERCAP is administered in the morning and simvastatin in the evening, as indicated for such medicine.

Diuretics and ACE inhibitors

Lercanidipine (contained in ZERCAP) has been safely administered with diuretics and ACE (angiotensin converting enzyme inhibitors) inhibitors.

Other medicines affecting blood pressure

Increased hypotensive effects may be observed when ZERCAP is administered with other medicines affecting blood pressure, such as beta-blockers which are metabolised in the liver (e.g. propranolol and

metoprolol), alpha-blockers for the treatment of urinary symptoms, tricyclic antidepressants, and 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 is no clinical experience with lercanidipine in pregnancy and lactation. ZERCAP should therefore not be prescribed during pregnancy or to women with child-bearing potential, unless effective contraception is used.

Breastfeeding

Because of the high lipophilicity of ZERCAP, distribution in milk may be expected. ZERCAP should therefore not be administered to mothers who are breastfeeding their babies.

Fertility

No clinical data are available with lercanidipine.

4.7 Effects on ability to drive and use machines

Dizziness, asthenia, fatigue and somnolence have been reported. Patients should be cautioned not to drive or handle machinery if these side effects occur.

4.8 Undesirable effects

a. Summary of the safety profile

The frequently reported adverse reactions are peripheral oedema, headache, flushing, tachycardia, and palpitations.

b. Tabulated list of adverse reactions

MedDRA System Organ Class/ **Frequency**	
Immune system disorders	
Less frequent:	Hypersensitivity, angioedema
Frequency unknown:	Angioedema
Psychiatric disorders	
Less frequent:	Somnolence, depression
Nervous system disorders	
Frequent:	Headache, dizziness
Less frequent:	Fatigue, syncope
Eye disorders	
Frequency unknown:	Eye pain
Cardiac disorders	
Frequent:	Tachycardia, palpitations
Less frequent:	Angina pectoris (see section 4.4)
Frequency unknown:	Precordial pain, myocardial infarction (see section 4.4)

Vascular disorders	
Frequent:	Flushing, peripheral oedema
Less frequent:	Hypotension
Gastrointestinal disorders	
Less frequent:	Nausea, dyspepsia, abdominal pain, diarrhoea, vomiting
Frequency unknown:	Gingival hypertrophy, peritoneal cloudy effluent
Hepatobiliary disorders	
Frequency unknown:	Increased serum hepatic transaminases (reversible)
Skin and subcutaneous tissue disorders	
Less frequent:	Rash, pruritus, urticaria
Musculoskeletal and connective tissue disorders	
Less frequent:	Myalgia
Renal and urinary disorders	
Less frequent:	Polyuria, pollakiuria
General disorders and administration site conditions	
Frequent:	Asthenia
Less frequent:	Fatigue, chest pain

c. Description of selected adverse reactions

Lercanidipine (contained in ZERCAP) does not appear to influence adversely blood sugar or serum lipid levels.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Patients with pre-existing angina pectoris may less frequently

experience increased frequency, duration, or severity of these attacks. 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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 .

4.9 Overdose

Symptoms

Excessive peripheral vasodilatation with marked hypotension and reflex tachycardia.

Treatment

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 24 hours at least.

Treatment is symptomatic and supportive.

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

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of Ca^{2+} 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 has 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.

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

5.2 Pharmacokinetic properties

Absorption

Lercanidipine is completely absorbed after 10 - 20 mg oral administration and peak plasma levels of 3,30 ng/mL ± 2,09 SD and 7,66 ng/mL ± 5,90 SD respectively, occur about 3 to 4 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 interconversion of enantiomers has been observed *in vitro*.

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.

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 lercanidipine may be increased.

The absolute bioavailability of orally administered lercanidipine is relatively low because of its 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.

Biotransformation

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.

Elimination

Elimination occurs essentially by biotransformation.

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.

Characteristics in specific groups

Elderly, renal and hepatic insufficiency

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 (about 70 %) levels of the medicine. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the medicine is normally metabolised extensively in the liver.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

10 mg film-coated tablets: Maize starch, sodium starch glycolate (Type A), colloidal anhydrous silica, cellulose microcrystalline (pH 113), poloxamer 188, sodium stearyl fumarate, macrogol 6000, hypromellose 6 cps, ferric oxide yellow (E172) and titanium dioxide (E171).

20 mg film-coated tablets: Cellulose microcrystalline (pH 112), maize starch, sodium starch glycolate (Type A), colloidal anhydrous silica, microcrystalline cellulose (pH 113), povidone (K-30), sodium stearyl fumarate, hypromellose 6 cps, macrogol 6000, ferric oxide red (E172) and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original package to protect from light.

6.5 Nature and contents of container

Blister pack using a white opaque PVC/PVdC film sealed with plain silver aluminium foil with heat seal lacquer coating. The blister strips are packed in cartons. Pack sizes: 2 x 14, 3 x 10, 6 x 10 & 10 x 10 tablets.

Not all pack sizes may be marketed at one time.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF REGISTRATION CERTIFICATES

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1,

Bassonia Estate Office Park (East),

1 Cussonia Drive,

Bassonia Rock Ext 12

Alberton, South Africa

8. REGISTRATION NUMBERS

ZERCAP 10: 52 / 7.1 / 0386

ZERCAP 20: 52 / 7.1 / 0387

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 September 2021

10. DATE OF REVISION OF THE TEXT

11 October 2023