1 **Professional Information**

SCHEDULING STATUS
S3

1. NAME OF THE MEDICINE

LERTENS 10 (Film coated tablets)

LERTENS 20 (Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LERTENS 10

Each film coated tablet contains:

Lercanidipine hydrochloride 10 mg

Sugar free

Sodium content: 0,788 mg per tablet

For the full list of excipients, see section 6.1.

LERTENS 20

Each film coated tablet contains:

Lercanidipine hydrochloride 20mg

Sugar free

Sodium content: 1,227 mg per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LERTENS 10

Yellow coloured, round shaped biconvex, film coated tablets with break-line on one side and plain on the other side.

LERTENS 20

Pink coloured, round shaped biconvex, film coated tablets with break-line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LERTENS 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.

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 (see section 4.4).

LERTENS is not recommended for use in patients with severe hepatic dysfunction or in patients with severe renal dysfunction (Glomerular Filtration Rate < 30 mL/min; creatinine clearance <10 mL/min) including patients undergoing dialysis;

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

For oral use.

4.3 Contraindications

- Hypersensitivity to lercanidipine, dihydropyridine or any other ingredient of **LERTENS** tablets listed in section 6.1.
- Untreated congestive cardiac failure
- Unstable angina pectoris or recent (within 1 month) myocardial infarction
- Patients with left ventricular outflow tract obstruction,
- Severe renal impairment (GFR < 30 mL/min), including patients undergoing dialysis
- Severe hepatic impairment

- Children under the age of 18 years
- Pregnancy and lactation, women of childbearing must use effective contraception (see section 4.6).
- **LERTENS** should not be taken with **Grapefruit or grapefruit juice** (see section 4.5)**.**
- Co-administration with strong inhibitors of CYP3A4, e.g. ketoconazole, ritonavir, itraconazole, erythromycin; troleandomycin, clarithromycin and fluoxetine (see section 4.5)
- Cyclosporin and **LERTENS** should not be administered together (see section 4.5)

4.4 Special warnings and precautions for use

Sick sinus syndrome

Special care should be exercised when **LERTENS** is used in patients with sick sinus syndrome (if a pacemaker is not in situ).

Left ventricular dysfunction

Although haemodynamic studies revealed no impairment of ventricular function, care is also required in patients with moderate to severe LV dysfunction, including LV outflow tract obstruction.

Ischaemic heart disease

Short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although **LERTENS** is 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 reported.

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 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 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 reported to be 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 medicine (see section 4.5)

Sodium

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

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

Contraindications of concomitant use

Inhibitors of CYP3A4:

Co-administration of **LERTENS** with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) is contraindicated (see section 4.3) and may cause 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)

Ciclosporin:

Ciclosporin and **LERTENS** should not be administered together (see section 4.3). Increased plasma levels of both lercanidipine and ciclosporin have been reported following concomitant administration.

Grapefruit or grapefruit juice:

LERTENS 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 and increased hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see section 4.3).

Concomitant use not recommended

Co-administration of **LERTENS** 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 should be avoided since it may potentiate the effects of **LERTENS** (see section 4.4).

Precautions including dose adjustment:

Substrates of CYP3A4

Caution should be exercised when **LERTENS** is co-prescribed with other substrates of CYP3A4 e.g. terfenadine, astemizole, Class III anti dysrhythmic medicines such as amiodarone and quinidine.

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam orally to elderly volunteers, lercanidipine's absorption has been reported to be 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 **LERTENS** was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of **LERTENS** 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, **LERTENS** 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 conducted between fluoxetine (an inhibitor of CYP2D6 and CYP3A4) and lecarnidipine 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 175 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.

Diuretics and ACE inhibitors

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Warfarin

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

Other medications affecting blood pressure

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

There is no clinical experience reported with **LERTENS** in pregnancy and lactation.

Pregnancy

LERTENS should not be administered during pregnancy or to women of child-bearing potential unless effective contraception is used (see **section 4.3**).

Breastfeeding

Because of high lipophilicity of lercanidipine, distribution in milk may be expected. **LERTENS** should therefore not be administered to nursing mothers (see section 4.3).

Fertility

No clinical data are available with lercanidipine.

4.7 Effects on ability to drive and use machines

Caution should be exercised as **LERTENS** may cause dizziness, asthenia, fatigue and less frequently somnolence; which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions reported in clinical trials and post-marketing studies were peripheral oedema, headache, flushing, tachycardia and palpitations.

System Organ Class	**Frequent**	**Less Frequent**	**Frequency unknown**
Immune system disorders		Hypersensitivity	
Nervous system disorders	Dizziness, headache.	Fatigue, syncope, somnolence	Mental depression
Eye disorders			Eye pain
Cardiac disorders	Tachycardia, peripheral oedema	Angina pectoris. Patients with pre-existing angina pectoris have reported an increase in frequency, duration or severity of these attacks	Palpitations, precordial pain, and myocardial infarction.
Vascular disorders	Flushing	Hypotension	

Gastro-intestinal system disorders		Nausea, dyspepsia, abdominal pain, diarrhoea, vomiting	Gingival hypertrophy Peritoneal cloudy effluent
Hepato-biliary disorders			Increase in serum levels of hepatic transaminases
Skin and subcutaneous disorders		Rash, pruritus, urticaria.	Gingival hyperplasia, angioedema.
Musculoskeletal and connective tissue disorders		Myalgia	
Renal and urinary disorders		Polyuria.	Increased micturition frequency.
General disorders and administration site conditions	Asthenia, peripheral oedema	Chest pain. Fatigue	

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 drug reactions to SAHPRA via the Med

Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000.

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

Over dosage 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. The most common ADRs associated to cases of overdose have been hypotension, dizziness, headache and palpitations.

Treatment

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. 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.

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

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

Paediatric population

No clinical data has been reported in the paediatric population.

5.2 Pharmacokinetic properties

Absorption

Lercanidipine has been reported to be 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 reported 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 **LERTENS** 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 **LERTENS** is ingested up to 2 hours after a high fat meal. Accordingly, **LERTENS** should be taken before meals.

Distribution

Distribution from plasma to tissues and organs has been reported to be rapid and extensive. The degree of serum protein binding of lercanidipine has been reported to exceed 98 %. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the medicine may be increased.

The absolute bioavailability of orally administered lercanidipine has been reported to be relatively low as a consequence of high first' pass metabolism.

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

Biotransformation

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

Oral administration of lercanidipine has been reported to lead to plasma levels of lercanidipine not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations were reported 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 has been reported for 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 has been reported.

Oral availability of lercanidipine has been reported to increase 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 has been reported to be similar to that reported in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients reported 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 medicine is normally metabolised extensively in the liver.

Elimination

Elimination occurs essentially by biotransformation**.** A mean terminal elimination half-life of 8-10 hours was calculated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline, colloidal silicon dioxide, ferric oxide red, ferric oxide yellow, hypromellose 6cps,

macrogol 6000, maize starch, methanol, poloxamer 188, povidone K-30, sodium starch glycolate, sodium; stearyl fumarate, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

Cartons containing 28 or 30 tablets packed in blister strips of 10 or 14 tablets each.

The blister strips comprise of white opaque PVC/PVdC film sealed with plain aluminum foil with heat seal lacquer coating.

Not all pack sizes may be marketed.

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 CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort, 1724

South Africa

Tel: +27(0) 12 643 2000

8. REGISTRATION NUMBERS

LERTENS 10: 50/7.1/0638

LERTENS 20: 50/7.1/0639

9. DATE OF FIRST AUTHORISATION

06 Jully 2021

10. DATE OF REVISION OF THE TEXT

02 January 2026

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