SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LERZAN 10 film coated tablets

LERZAN 20 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITON

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

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

LERZAN is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LERZAN 10 are yellow coloured, round shaped biconvex, film coated tablets with a break-line on one side and plain on the other side.

LERZAN 20 are pink coloured, round shaped biconvex, film coated tablets with a break-line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

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 mild to moderate 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.

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

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 hydrochloride, dihydropyridine or any of the other ingredients of LERZAN listed in section 6.1.
- 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 (including patients undergoing dialysis) 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.
- LERZAN is contraindicated during pregnancy and lactation (see section 4.6).
- LERZAN should not be taken with grapefruit juice.
- Co-administration of LERZAN with inhibitors of CYP3A4 e.g. ketoconazole, itraconazole, erythromycin, ritonavir, troleandomycin and fluoxetine are contraindicated.
- Cyclosporin and LERZAN should not be administered together.

4.4 Special warnings and precautions for use

Sick sinus syndrome and left ventricular dysfunction

Special care should be exercised when LERZAN 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 also required in patients with moderate to severe LV dysfunction.

Ischaemic heart disease

Short-acting dihydropyridine may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although LERZAN is a long-acting dihydropyridine, caution is required in these 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.

Use in renal or hepatic impairment

Special care should be exercised when treatment is commended in patients with mild to moderate renal or hepatic dysfunction. Although the usually recommended dose schedule of 10 mg daily 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 section 4.2). LERZAN is contraindicated in patients with severe hepatic impairment or in patients with severe renal impairment (GFR < 30mL/min), including patients undergoing haemodialysis (see section 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 LERZAN 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).

Paediatric population

The safety and efficacy of LERZAN 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.

Inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, fluoxetine, clarithromycin) are contraindicated (see section 4.3).

Ciclosporin

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

Grapefruit or grapefruit juice

Lercanidipine 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.
LERZAN should not be taken with grapefruit juice (see section 4.3).

Concomitant use not recommended

Inducers of CYP3A4

Co-administration of LERZAN with inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, phenobarbitone, 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.

Alcohol

Alcohol should be avoided since it may potentiate the effects of LERZAN (see section 4.4).

Precautions including dose adjustment

Substrates of CYP3A4

Caution should be exercised when LERZAN is co-prescribed with other substrates of CYP3A4 e.g. terfenadine, astemizole, class Ill antidysrhythmic medicines such as amiodarone and quinidine, sotalol.

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's 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.

Beta-blockers

Caution should be exercised when combining LERZAN with beta-adrenergic blocking medicines which are metabolised in the liver (such as propranolol and metoprolol) as there is a risk of increased hypotensive effect.
When lercanidipine was co-administered with metoprolol, 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 Beta-blockers and may therefore occur with other medicines of this class. Consequently, LERZAN may be safely administered with Beta-adrenoceptor blocking medicines, but dose adjustment may be required.

Digoxin

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

Concomitant use with other medicines

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 LERZAN 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 Beta-hydroxyacid by 28 %. It is unlikely that such changes are of clinical relevance. No interaction is expected when LERZAN 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.

Other medicines affecting blood pressure

An increased hypotensive effect may be observed when LERZAN 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 is no clinical experience with lercanidipine in pregnancy and lactation. Studies in animals have not shown teratogenic effects (see section 5.3), but these have been observed with other dihydropyridine compounds.
LERZAN should therefore not be taken during pregnancy or by woman of child-bearing potential unless effective contraception is used.

Breastfeeding:

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

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

LERZAN has minor influence on the ability to drive and use machines. However, caution should be exercised because dizziness, asthenia, fatigue and somnolence may occur.

4.8 Undesirable effects

Summary of the safety profile

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

System Organ Class	**Frequency**	**Side effects**

Immune system disorders	Less frequent Frequency unknown	Hypersensitivity Angioedema
Nervous system disorders	Frequent Less frequent	Headache Dizziness, somnolence, syncope, mental depression
Eye disorders	Less frequent	Eye pain
Cardiac disorders	Frequent Less frequent	Tachycardia, palpitations Angina pectoris, precordial pain, myocardial infarction, chest pain
Vascular Disorders	Frequent Less frequent	Flushing, peripheral oedema Hypotension
Gastrointestinal disorders	Less frequent Frequency unknown	Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, gingival hyperplasia Peritoneal cloudy effluent
Hepato-biliary disorders	Less frequent	Isolated and reversible increases in serum levels of hepatic transaminases
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, increased micturition frequency,

		pollakiuria
General disorders and administration site conditions	Less frequent	Asthenia, fatigue

Reporting of suspected adverse reactions:

Reporting of 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 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

Lercanidipine overdosage might be expected to cause 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 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.
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

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

5.2 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 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 CYP3A4; 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 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 revealed 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:

Cellulose microcrystalline

Colloidal anhydrous silica

Macrogol 6000

Maize Starch

Sodium starch glycolate

Sodium stearyl fumarate

LERZAN 10 also contains poloxamer 188 and LERZAN 20 also contains povidone (K-30)

Film coating:

Hypromellose

Macrogol 6000

Titanium dioxide

LERZAN 10 also contains ferric oxide yellow and LERZAN 20 also contains ferric oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

White opaque PVC/PVdC blisters film sealed with plain aluminium foil. The blister strips are packed in cartons.

Pack size: 30 or 60 film coated tablets.

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

Activo Health (Pty) Ltd.

Block B

Arena Office Park

272 West Avenue

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0157

South Africa

8. REGISTRATION NUMBERS

LERZAN 10: 50/7.1/0663

LERZAN 20: 50/7.1/0664

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 February 2021

10. DATE OF REVISION OF THE TEXT

07 February 2025