APPROVED PROFESSIONAL INFORMATION FOR NIDEXIF

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

NIDEXIF 10 mg (film coated tablet)

NIDEXIF 20 mg (film coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NIDEXIF 10 mg

Each film-coated tablets contains 10 mg of lercanidipine hydrochloride (as hemihydrate).

NIDEXIF 20 mg

Each film-coated tablets contains 20 mg of lercanidipine hydrochloride (as hemihydrate).

Contains sugar “lactose monohydrate”

Each 10 mg film-coated tablets contains 29,861 mg of lactose monohydrate.

Each 20 mg film-coated tablets contains 59,722 mg of lactose monohydrate.

3 PHARMACEUTICAL FORM

NIDEXIF 10 mg

Yellow, film coated, round shaped, biconvex tablets debossed with “3” and “4” on either side of score line on one side of the tablet and “HL” on the other side.

NIDEXIF 20 mg

Pink to peach, film coated, round shaped, biconvex tablets debossed with “3” and “5” on either side of the score line on one side of tablet and “HL” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIDEXIF 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.

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

Method of administration

Orally at least 15 minutes before a meal.

4.3 Contraindications

- Hypersensitivity to the lercanidipine hydrochloride, to any dihydropyridine or to any of the excipients listed in section 6.1.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Within 1 month of a myocardial infarction.
- Severe hepatic impairment.
- Severe renal impairment (GFR < 30 mL/min, including patients undergoing dialysis.
- Co-administration with:
    - strong inhibitors of CYP3A4 (see section 4.5),
    - cyclosporin (see section 4.5),
    - grapefruit juice (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used.

4.4 Special warnings and precautions for use

Sick sinus syndrome

Lercanidipine should be administered with caution in patients with sick sinus syndrome (without a pacemaker).

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 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 (see section 4.8).

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 should 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 sections 4.2 and 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 lercanidipine 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).

Lactose

NIDEXIF contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take NIDEXIF.

Sodium

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

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

Grapefruit or grapefruit juice

As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit or grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see section 4.3).

Concomitant use not recommended

Inducers of CYP3A4

Co-administration of lercanidipine with CYP3A4 inducers 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 (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 lercanidipine is co-prescribed with other substrates of CYP3A4, like terfenadine, astemizole, class III antiarrhythmic drugs such as amiodarone, quinidine, sotalol.

Midazolam

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

Metoprolol

When lercanidipine 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, lercanidipine 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 with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± s.d.), 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 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.

Other medications affecting blood pressure

As for all antihypertensive medications, an increased hypotensive effect may be observed when lercanidipine is administered with other medications 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 NIDEXIF in pregnancy and lactation; NIDEXIF should therefore not be administered during pregnancy or to woman with child-bearing potential unless effective contraception is used.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

NIDEXIF 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Immune system disorders	Less frequent	Hypersensitivity
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, somnolence, syncope, mental depression
Eye disorders	Less frequent	Eye pain
Cardiac disorders	Frequent	Tachycardia, palpitations
	Less frequent	angina pectoris, precordial pain, myocardial infarction, chest pain
Vascular disorders	Less frequent	Flushing, hypotension, oedema peripheral
Gastrointestinal disorders	Less frequent	Dyspepsia, nausea, abdominal pain upper, vomiting diarrhoea, gingival hypertrophy[1], peritoneal cloudy effluent[1]
Hepatobiliary disorders	Less Frequent	Isolate and reversible serum transaminase increased[1]

Skin and subcutaneous tissue disorders	Less Frequent	Rash, pruritus, urticaria, angioedema[1]
Musculoskeletal and connective tissue disorders	Less Frequent	Myalgia
Renal and urinary disorders	Less Frequent	Polyuria, pollakiuria, increased micturition frequency
General disorders and administration site conditions	Less Frequent	Asthenia, fatigue, chest pain

Lercanidipine does not appear to influence adversely blood sugar or serum lipid levels.

[1]adverse reactions from spontaneous reporting in the worldwide post-marketing experience.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NIDEXIF is important. It allows continued monitoring of the benefit/risk balance of NIDEXIF. Healthcare 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 or to the Holder of certificate of registration through the mail: **pvg.cdma@hererodrugs.com.**

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Selective calcium channel blockers with mainly vascular effects – Dihydropyridine derivatives.

ATC code: C08CA13

CATEGORY AND CLASS

A 7.1 Vasodilators, hypotensives.

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 total 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 vasodilatation induced by Lercanidipine HCl is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients. As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Paediatric population

No clinical trial has been performed in the paediatric population.

5.2 Pharmacokinetic properties

Absorption

Lercanidipine HCl is completely absorbed after 10-20 mg oral administration and peak plasma levels, 3,30 ng/mL ± 2,09 s.d. and 7,66 ng/mL ± 5,90 s.d. respectively, occur about 3 - 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 "*in vivo*" interconversion of enantiomers is observed.

Due to the high first pass metabolism, the absolute bioavailability of Lercanidipine HCl 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 Lercanidipine HCl is ingested up to 2 hours after a high fat meal. Accordingly, Lercanidipine HCl 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 the drug may be increased.

Biotransformation

Lercanidipine HCl is extensively metabolised by CYP3A4; no parent drug 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. "*In vitro*" experiments with human liver microsomes have demonstrated that lercanidipine shows some degree of inhibition of CYP3A4 and CYP2D6, at concentrations 160- and 40-fold, respectively, higher than those reached at peak in the plasma after the dose of 20 mg.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, inhibition of biotransformation of medicines metabolised by CYP3A4 and CYP2D6 by Lercanidipine HCl is not expected at therapeutic doses.

Elimination

Elimination occurs essentially by biotransformation. The pharmacokinetic half-life is 3 to 5 hours, but the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

Linearity/non linearity

Oral administration of Lercanidipine HCl 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.

Special populations

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 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

- Lercanidipine hydrochloride
- Lactose monohydrate
- Cellulose microcrystalline
- Sodium starch glycolate
- Povidone (k-30)

Composition of Opadry II yellow 85F520410

- Polyvinyl alcohol-part hydrolyzed E1203
- Titanium dioxide E171
- Macrogol/PEG E1521
- Talc E553b
- Iron oxide yellow E172
- Iron oxide red E172

Composition of Opadry II pink 85F540460

- Polyvinyl alcohol-part hydrolyzed E1203
- Titanium dioxide E171
- Macrogol/PEG E1521
- Talc E553b
- Iron oxide red E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C

Protect from moisture.

Keep the tablets in the original container until required for

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10 x 10's Aclar-Alu Blister

White opaque 250 µ PVC/102 µ Aclar film with 0,025 mm Plain aluminium foil (Hard Tampered) with 7GSM HSL coating on bright side.

9 x 10's Alu-Alu Blister

Form pack film with Desiccant with 20 µ Plain aluminum foils with 15GSM PE coating on bright side width 148 mm (sealable to form pack film with desiccant).

500's simulated Bulk Pack

Clear 100 µ poly bag 9 x 12 inches with triple laminated bag (9"x12") with silica gel sachet 5 gram.

6.6 Special precautions for disposal and other handling

'No special requirements'

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No.2, First Floor

74 Waterfall Drive

Midrand, 2066

Telephone number: 012 644 1220

e-mail address: nokuthula.n@hetero.com

8 REGISTRATION NUMBER(S)

NIDEXIF 10 mg: 57/7.1/0045.043

NIDEXIF 20 mg: 57/7.1/0046.044

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

08 July 2025

10 DATE OF REVISION OF THE TEXT