PROFESSIONAL INFORMATION FOR CIPALAT XR

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CIPALAT XR 30 extended release tablets.

CIPALAT XR 60 extended release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CIPALAT XR 30 tablet contains 30 mg nifedipine.

Each CIPALAT XR 60 tablet contains 60 mg nifedipine.

CIPALAT XR is sugar free.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Extended release tablets

CIPALAT XR 30

Pink coloured, film-coated circular biconvex tablet having an orifice on one side and plain on the other.

CIPALAT XR 60

Pink coloured, film-coated circular biconvex tablet having an orifice on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPALAT XR is indicated for the:

- Treatment of mild to moderate hypertension.
- Prophylaxis of chronic stable angina pectori**s.**

4.2 Posology and method of administration

Posology

Adults:

The recommended initial dose is one 30 mg tablet once daily. The dose may be increased according to individual requirements up to a maximum of 90 mg once daily. Titration steps should proceed over a 7 to 14 days period so that the response to each dose level can be assessed before proceeding to higher doses.

Special populations

Patients with Renal Impairment:

Dosage adjustments should not be required for patients with impaired renal function.

Patients with hepatic impairment

Owing to the duration of action of the formulation, CIPALAT XR should not be administered to patients with hepatic impairment (see **section 4.3**).

Elderly:

A slight alteration of the pharmacokinetics of CIPALAT XR may be seen in the elderly. However, dosage adjustment in these patients is not usually necessary.

Paediatric population:

The safety and efficacy of CIPALAT XR in children below 18 years has not been established.

Method of administration:

Oral use.

CIPALAT XR tablets should be swallowed whole with a glass of water and not bitten, broken up or chewed.

Grapefruit juice is to be avoided.

It is recommended that each dose of CIPALAT XR should be taken at approximately 24 hours intervals i.e. at the same time each day, preferably in the morning. CIPALAT XR may be taken independently of mealtimes.

4.3 Contraindications

Known hypersensitivity to nifedipine or to other dihydropyridines because of the theoretical risk of cross-reactivity or any other ingredient of CIPALAT XR listed in **section 6.1**.

CIPALAT XR must not be used in patients with clinically significant aortic stenosis, in cardiogenic shock, unstable angina or within one month of a myocardial infarction.

CIPALAT XR should not be used for the treatment of acute attacks of angina. The safety of CIPALAT XR in malignant hypertension has not been established.

CIPALAT XR should not be used for secondary prevention of myocardial infarction.

Due to the duration of action of the formulation, CIPALAT XR should not be used in patients with hepatic impairment (see **section 4.4**).

CIPALAT XR should not be administered to patients with a history of gastrointestinal obstruction, oesophageal obstruction or any degree of decreased lumen diameter of the gastrointestinal tract.

CIPALAT XR is contraindicated in patients with inflammatory bowel disease. CIPALAT XR should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction by rifampicin.

CIPALAT XR is contraindicated in pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

CIPALAT XR tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Grapefruit juice inhibits the metabolism of CIPALAT XR. After regular intake of grapefruit juice the blood pressure lowering effect may last for at least 3 days after the last ingestion of grapefruit juice (see **section 4.5**).

Caution should be exercised in patients with hypotension as there is a risk of further reduction in blood pressure. Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg), in cases of manifest heart failure and in cases of severe aortic stenosis.

The following medicines are known to either inhibit or to induce cytochrome P450 3A4 system and may therefore alter the first pass or clearance of nifedipine

Digoxin, phenytoin, quinidine, quinupristin, dalfopristin, cimetidine, rifampicin, diltiazem, cisapride, macrolide antibiotics (e.g., erythromycin), fluoxetine, anti-HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), azole antimycotics (e.g. ketoconazole, itraconazole, fluconazole), nefazodine, tacrolimus, carbamazepine, phenobarbitone and valproic acid. See **section 4.5)**

Upon co-administration with these medicines, the blood pressure should be monitored and, if necessary, a reduction of the CIPALAT XR dose should be considered.

CIPALAT XR is contraindicated in pregnancy (see **section 4.3** and **section 4.6**). However, care must be exercised in pregnant women when administering CIPALAT XR in combination with intravenous magnesium sulphate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy, refer to **section 4.6**

Safety of CIPALAT XR as tocolytic medicine and in the treatment of hypertension in pregnancy after 20 weeks has not been established. Harm to the foetus cannot be excluded.

CIPALAT XR is contraindicated for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see **section 4.6**).

CIPALAT XR is contraindicated in patients with hepatic impairment (see **section 4.2** and **4.3**).

CIPALAT XR may be used in combination with beta-blocking medicines and other antihypertensive medicines but the possibility of an additive effect resulting in postural hypotension should be taken into consideration.

CIPALAT XR will not prevent possible rebound effects after cessation of other antihypertensive therapy.

CIPALAT XR should not be switched once a patient has been stabilised, without appropriate monitoring. Diabetic patients taking CIPALAT XR may require adjustment of their control. Care should be exercised in dialysis patients with malignant hypertension and irreversible kidney failure with hypovolaemia as a marked fall in blood pressure may occur.

A transient increase in blood glucose has been noted. Care must be taken in patients with diabetes mellitus.

CIPALAT XR should be used with caution in patients with a poor cardiac reserve. Deterioration of heart failure has occasionally been observed with nifedipine.

In single cases obstructive gastrointestinal symptoms have been described without known history of gastrointestinal disorders.

Upon swallowing, the biologically inert components of the CIPALAT XR tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell and appears to be the complete tablet and may be seen in the toilet or associated with the patient's stools. Also, as a result of this, care should be exercised when administering CIPALAT XR to patients, as obstructive symptoms may occur. Bezoars can occur and may require surgical intervention.

CIPALAT XR must not be used in patients with Kock pouch (ileostomy after proctocolectomy).

When doing barium contrast X-ray, CIPALAT XR may cause false positive effects (e.g. filling defects interpreted as polyp).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say 'sodium-free'.

4.5 Interactions with other medicines and other forms of interaction

CIPALAT XR is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Medicines that are known to either inhibit or induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of CIPALAT XR **(**see **section 4.4)**.

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to CIPALAT XR should be monitored and, if necessary, an increase in the CIPALAT XR dose considered. If the dose of CIPALAT XR is increased during co-administration of both medicines, a reduction of the CIPALAT XR dose should be considered when the treatment is discontinued.

The extent as well as the duration of interactions should be taken into account when administering CIPALAT XR together with the following medicines:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of CIPALAT XR is distinctly reduced and thus its efficacy weakened. The use of CIPALAT XR in combination with rifampicin is therefore contra-indicated (see section **4.3**).

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered (see **sections 4.2 and 4.4**). In the majority of these cases, no formal studies to assess the potential for a medicine interaction between nifedipine and the medicine(s) listed have been undertaken, thus far.

Erythromycin: Erythromycin is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, the potential for an increase of CIPALAT XR plasma concentrations upon co-administration of both medicines cannot be excluded.

Amprenavir, indinavir, nelfinavir, ritonavir, saquinavir: A clinical study investigating the potential of an interaction between CIPALAT XR and indinavir, nelfinavir, ritonavir or saquinavir has not yet been performed. Medicines of this class are known to inhibit the cytochrome P450 3A4 system. In addition, indinavir and ritonavir have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of CIPALAT XR. When administered together with CIPALAT XR, a substantial increase in plasma concentrations of CIPALAT XR due to a decreased first pass metabolism and a decreased elimination cannot be excluded. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Ketoconazole, itraconazole, fluconazole: Medicines of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with CIPALAT XR a substantial increase in systemic bioavailability of CIPALAT XR due to decreased first pass metabolism cannot be excluded. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Fluoxetine: Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of CIPALAT XR. Therefore an increase of CIPALAT XR plasma concentrations upon co-administration of both medicines cannot be excluded. When fluoxetine is given together with CIPALAT XR, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Nefazodone: A clinical study investigating the potential of an interaction between CIPALAT XR and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, an increase of CIPALAT XR plasma concentrations upon co-administration of both medicines cannot be excluded. When nefazodone is given together with CIPALAT XR, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Quinupristin / Dalfopristin: Simultaneous administration of quinupristin/dalfopristin and CIPALAT XR may lead to increased plasma concentrations of CIPALAT XR. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Valproic acid: As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in CIPALAT XR plasma concentrations cannot be excluded.

Cimetidine: Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentration of CIPALAT XR and may potentiate the antihypertensive effect.

Cisapride: Simultaneous administration of cisapride and CIPALAT XR may lead to increased plasma concentrations of CIPALAT XR. Upon co-administration, the blood

pressure should be monitored and, if necessary, a reduction in the CIPALAT XR dose considered.

Phenytoin: Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of CIPALAT XR is reduced and thus its efficacy weakened. When both medicines are concomitantly administered, the clinical response of CIPALAT XR should be monitored and, if necessary, an increase of the CIPALAT XR dose considered. If the dose of CIPALAT XR is increased during co-administration of both medicines, a reduction of the CIPALAT XR dose should be considered when the treatment with phenytoin is discontinued.

Carbamazepine: As carbamazepine has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in CIPALAT XR plasma concentrations and hence an increase in efficacy cannot be excluded.

Phenobarbitone: As phenobarbitone has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in CIPALAT XR plasma concentrations and hence an increase in blood levels cannot be excluded.

Effects of CIPALAT XR on other medicines:

CIPALAT XR may increase the blood pressure lowering effect on concomitant applied antihypertensives, such as:

- Diuretics
- β-blockers
- ACE-inhibitors
- AT1-antogonists/Angiotensin 1 receptor blockers
- Other calcium antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa

When CIPALAT XR is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since severe hypotension can occur. Deterioration of heart failure is also known to develop.

Digoxin: The simultaneous administration of CIPALAT XR and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin**.** The patient should therefore be checked for symptoms of digoxin toxicity as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine: When CIPALAT XR and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of CIPALAT XR, a distinct increase in plasma concentrations of quinidine has been observed in individual cases. For this reason, when

CIPALAT XR is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose is recommended. The blood pressure should be carefully monitored if quinidine is added to an existing therapy with CIPALAT XR. If necessary, the dose of CIPALAT XR, should be decreased.

Tacrolimus: Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Upon co-administration of tacrolimus and CIPALAT XR, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Diltiazem: Diltiazem decreases the clearance of CIPALAT XR. CIPALAT XR increases the bioavailability and decreases the clearance of diltiazem. The combination of both medicines should be administered with caution and a reduction of both doses may be considered.

Grapefruit juice: Grapefruit juice inhibits the metabolism of CIPALAT XR. Administration of CIPALAT XR together with grapefruit juice thus results in elevated plasma concentrations of CIPALAT XR due to a decreased first pass metabolism in the gastrointestinal tract. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking CIPALAT XR (see **section 4.2**).

Other forms of interactions:

CIPALAT XR may cause falsely increased spectrophtometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy

CIPALAT XR is contraindicated during pregnancy (see **section 4.3**). In animal studies, nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity when administered during any stage of pregnancy and decreased neonatal survival after birth. Co-administration of CIPALAT XR with I.V. magnesium sulphate may cause an excessive fall in blood pressure which could harm both mother and foetus.

Breastfeeding

CIPALAT XR is contraindicated during breastfeeding (see **section 4.3)**. Nifedipine is excreted in the breast milk.

Fertility

In single cases of in vitro fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by in vitro fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

4.7 Effects on ability to drive and use machines

Reactions to CIPALAT XR, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery (see **section 4.8**). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8 Undesirable effects

The following adverse drug reactions (ADRs) can occur:

Tabulated list of adverse reactions

MedDRA system organ class	Frequency	Side effects
Immune system disorders	Less frequent	Allergic reaction, allergic oedema/angioedema (incl. larynx oedema*), pruritus, urticaria, rash
Psychiatric disorders	Less frequent	Anxiety reactions, sleep disorders
Nervous system disorders	Frequent	Headache
	Less frequent	Vertigo, migraine, dizziness. tremor, paraesthesia/dysaesthesia, somnolence
Eye disorders	Frequent	Eye pain
	Less frequent:	Visual disturbances, amblyopia
Cardiac disorders	Less frequent	Tachycardia, palpitations, chest pain (angina pectoris)
Vascular disorders	Frequent	Oedema (incl. peripheral oedema), vasodilatation
	Less frequent	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Less frequent	Nosebleed, nasal congestion
Gastrointestinal disorders	Frequent	Constipation
	Less frequent	Gastrointestinal and abdominal pain, vomiting, nausea, dyspepsia, flatulence, dry mouth, gingival hyperplasia, gastroesophageal reflux, gastroesophageal sphincter insufficiency.

Hepato-biliary disorders	Less frequent:	Transient increase in liver enzymes
Skin and subcutaneous tissue disorders	Less frequent	Erythema, palpable purpura
Musculoskeletal and connective tissue disorders	Less frequent	Muscle cramps, joint swelling, arthralgia, myalgia
Renal and urinary disorders	Less frequent:	Polyuria, dysuria
Reproductive system and breast disorders	Less frequent	Erectile dysfunction
General disorders and administration site conditions	Frequent:	Feeling unwell
	Less frequent:	Unspecific pain, chills
* = may result in life-threatening outcome		

Post-marketing experience

The ADRs for which a frequency could not be estimated (frequency unknown), are listed below:

MedDRA system Organ Class	**Side effects**
Blood and lymphatic system disorders	Agranulocytosis Leucopenia
Immune system disorders	Anaphylactic/anaphylactoid reaction
Endocrine disorders	Gynaecomastia

Metabolism and nutrition disorders	Hyperglycaemia
Nervous system disorders	Hypoaesthesia
Respiratory, thoracic and mediastinal disorders	Dyspnoea Pulmonary oedema**
Gastrointestinal disorders	Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting
Hepato-biliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis Photosensitivity allergic reaction
**cases have been reported when used as tocolytic during pregnancy (see section 4.6)	

Description of selected adverse reactions

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

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 the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

The following symptoms are observed in cases of severe nifedipine intoxication: Flushing, headaches, severe hypotension, increase or decrease in heart rate, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema and unconsciousness to the point of coma have been observed.

Treatment

Particularly in cases of intoxication with prolonged release products like CIPALAT XR elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Treatment is symptomatic and supportive.

Bradycardiac heart rhythm disturbances may be treated symptomatically with ß-sympathomimetics and in life-threatening bradycardiac disturbances of heart rhythm, temporary pacemaker therapy is advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10 – 20 mL of a 10 % calcium gluconate solution administered intravenously and repeated if necessary). As a result, the serum calcium may reach the upper normal to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or norepinephrine (noradrenaline) may be administered additionally.
The dosage of these medicines is determined solely by the effect obtained.

Haemodialysis serves no purpose as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Additional liquid or volume must be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION

Category and class: A 7.1 Vasodilators, hypotensive medicines.
Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives.

ATC Code: C08CA05

5.1 Pharmacodynamic properties

Nifedipine, a calcium antagonist, improves oxygen supply to the myocardium with simultaneous decrease of oxygen requirements.

Nifedipine has a vasodilatory effect on the peripheral arterial beds causing a fall in peripheral resistance and an increase in peripheral blood flow. Ca^{2+} -channel blockers are useful in low-renin hypertension. Nifedipine dilates sub-maximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

5.2 Pharmacokinetic properties

CIPALAT XR tablets are formulated to release nifedipine at an approximately constant rate over 24 hours.

Upon swallowing, the biologically inert components of the CIPALAT XR tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell and appears to be the complete tablet and may be seen in the toilet or associated with the patient's stools.

Absorption

Nifedipine is well and completely absorbed from the gastrointestinal tract after oral administration. However, due to extensive hepatic first pass metabolism in the liver, the resultant bioavailability is about 45 % to 60 %.

Distribution

Nifedipine is about 92 to 98 % bound to plasma proteins.

Biotransformation

Nifedipine is extensively and rapidly metabolised in the liver with a prominent first-pass effect.

Elimination

About 80 % of the administered dose of nifedipine is excreted via the kidneys, mostly as its active metabolites. The rest (20 %) is excreted via the bile in the faeces.

Characteristics in patients

There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.

In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. CIPALAT XR should not be administered in these patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose acetate,

Ferric oxide,

Hydroxyl propyl methyl cellulose,

Hypromellose,

Magnesium stearate,

Polyethylene glycol,

Polyethylene oxide,

Sodium chloride,

Talc

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

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

6.5 Nature and contents of container

CIPALAT XR 30

Tablets are packed in plain aluminium and clear PVC/PE/PVDC blisters containing 14 or 15 tablets per blister placed in a carton

Pack size: 28’s, 30’s

Not all pack sizes are necessarily marketed.

CIPALAT XR 60

Tablets are packed in plain aluminium and clear PVC/PE/PVDC blisters containing 14 or 15 tablets per blister placed in a carton

Pack size: 28’s, 30’s

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and handling

No additional information.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 2,

Junxion Park

10 Elephant Lane,

Century City, 7441

Customer Care: 080 222 6662

8. REGISTRATION NUMBER (S)
CIPALAT XR 30: 50/7.1/0617

CIPALAT XR 60: 50/7.1/0618

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

First authorisation: 20 April 2017

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

06 February 2026