Professional Information for BIO NIFEDIPINE XL 30 / 60

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BIO NIFEDIPINE XL 30 prolonged-release tablets

BIO NIFEDIPINE XL 60 prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BIO NIFEDIPINE XL 30: Each prolonged-release tablet contains 30 mg nifedipine.

BIO NIFEDIPINE XL 60: Each prolonged-release tablet contains 60 mg nifedipine.

Sugar free.

Excipients with known effect

Sodium chloride and potassium chloride.

Each 30 mg tablet contains 9,52 mg sodium and 1,73 mg potassium.

Each 60 mg tablet contains 19.04 mg sodium and 3,46 mg potassium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

BIO NIFEDIPINE XL 30: Brown coloured, round biconvex film coated tablet free from cracks, plain on one side & laser drilled hole on other side.

BIO NIFEDIPINE XL 60: Brown coloured, round biconvex film coated tablet free from cracks, plain on one side & laser drilled hole on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate hypertension.

Prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

BIO NIFEDIPINE XL should be swallowed whole with a glass of water. Under no circumstances should the tablets be bitten, chewed or broken up.

The tablets should be taken at approximately 24 hour intervals, i.e. at the same time every day, preferably in the morning. BIO NIFEDIPINE XL can be taken irrespective of meal times.

The recommended initial dose is 30 mg once daily. If necessary, the dosage can be increased according to individual requirements up to a maximum of 90 mg once daily.

In general, titration steps should proceed over a 7 to 14 day period so that the response to each dose level can be assessed before proceeding to higher doses.

Special populations

Children and adolescents

The safety and efficacy of BIO NIFEDIPINE XL in children below 18 years has not been established.

Elderly patients

Based on pharmacokinetic data for BIO NIFEDIPINE XL no dose adjustment in elderly people above 65 years is necessary.

Patients with hepatic impairment

Owing to the duration of action of the formulation, BIO NIFEDIPINE XL should not be administered to

patients with hepatic impairment (see section 4.3).

Patients with renal impairment

Based on pharmacokinetic data no dosage adjustment is required in patients with renal impairment.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to nifedipine or to any of the excipients of BIO NIFEDIPINE XL listed in section 6.1.
- Pregnancy and breastfeeding.
- Clinically significant aortic stenosis, cardiovascular shock, unstable angina or during or within one month of a myocardial infarction.
- 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 the case of severe aortic stenosis.
- Hepatic impairment.
- History of gastrointestinal obstruction, oesophageal obstruction or any degree of decreased lumen diameter of the gastrointestinal tract.
- Patients with a Kock pouch (ileostomy after proctocolectomy).
- Inflammatory bowel disease or Crohn's disease.
- Concomitant use with rifampicin since effective plasma levels of nifedipine may not be obtained because of enzyme induction by rifampicin (see section 4.5).

4.4 Special warnings and precautions for use

Grapefruit juice inhibits the metabolism of BIO NIFEDIPINE XL. 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. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking BIO NIFEDIPINE XL (see section 4.5).

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, erythromycin, fluoxetine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, fluconazole, nefazodone, tacrolimus, carbamazepine, phenobarbitone and valproic acid. Upon co-administration with these medicines, the blood pressure should be monitored and if necessary, a reduction of the nifedipine dose should be considered.

Co-administration of BIO NIFEDIPINE XL with intravenous (I.V.) magnesium sulfate may cause an excessive fall in blood pressure.

The safety of nifedipine as tocolytic agent and in the treatment of hypertension in pregnancy after 20 weeks has not been established. Harm to the fetus cannot be excluded.

Although a "coronary steal" effect has not been demonstrated, BIO NIFEDIPINE XL therapy should be discontinued in patients experiencing this effect.
BIO NIFEDIPINE XL should not be switched once a patient has been stabilised, without appropriate monitoring.

Care should be exercised in dialysis patients with malignant hypertension and irreversible kidney failure with hypovolaemia should be closely monitored as a marked fall in blood pressure may occur.

As BIO NIFEDIPINE XL can cause an increase in blood glucose, care must be taken in patients with diabetes mellitus.

Symptoms of gastrointestinal obstruction have occurred in patients without a history of gastrointestinal disorders. Bezoars can occur in rare cases and may require surgical intervention.

BIO NIFEDIPINE XL must not be used in patients with Kock pouch (ileostomy after proctocolectomy).

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

Safety and efficacy in children have not been established.

Cases of *in vitro* fertilisation, nifedipine has been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In men who are repeatedly unsuccessful in fathering a child by in vitro fertilisation and if no other explanation can be found, nifedipine should be considered a possible reason.

BIO NIFEDIPINE XL can enhance or supplement the action of blood pressure lowering preparations such as beta-receptor blockers and diuretics. An additive effect resulting in postural hypotension should be considered. Blood pressure should be monitored carefully during initiation and upward titration of BIO NIFEDIPINE XL especially if patients are on antihypertensive therapy.

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

BIO NIFEDIPINE XL should be used with caution in patients with poor cardiac reserve, in angina patients with hypotension, patients with heart failure and in the case of severe aortic stenosis.

Excipients

BIO NIFEDIPINE XL 30 contains 9,52 mg of sodium and BIO NIFEDIPINE XL 60 contains 19,04 mg

of sodium.

Increasing the daily dose to 90 mg nifedipine results in an intake of 28,56 mg sodium. This is equivalent to 1,43 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Nifedipine, such as contained in BIO NIFEDIPINE XL 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 to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine.

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

Rifampicin

The co-administration of rifampicin and BIO NIFEDIPINE XL, distinctly reduces the bioavailability of BIO NIFEDIPINE XL and thus lowering the efficacy. The use of rifampicin with BIO NIFEDIPINE XL is therefore contraindicated (see section 4.3).

Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and if necessary, a reduction in the BIO NIFEDIPINE XL dose considered.

Erythromycin

Erythromycin is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. The potential for increase in nifedipine plasma concentrations upon co-administration should be considered.

Amprenavir, indinavir, nelfinavir, ritonavir, saquinavir

This class of medicines is known to inhibit the cytochrome P450 3A4 system. *In vitro*, indinavir and ritonavir have been shown to inhibit the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with BIO NIFEDIPINE XL, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded. If co-administered, blood pressure should be monitored and if necessary a dose reduction of BIO NIFEDIPINE XL be considered.

Ketoconazole, itraconazole, fluconazole

This class of medicine inhibits the cytochrome P450 3A4 system. When administered orally together with BIO NIFEDIPINE XL a substantial increase in bioavailability of nifedipine due to decreased first pass metabolism cannot be excluded. If co-administered, blood pressure should be monitored and if necessary a dose reduction of BIO NIFEDIPINE XL be considered.

Fluoxetine

Fluoxetine has been shown to inhibit the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase in plasma concentrations of nifedipine upon co-administration cannot be excluded. If co-administered, blood pressure should be monitored and if necessary a dose reduction of BIO NIFEDIPINE XL be considered.

Nefazodone

Nefazodone is known to inhibit the cytochrome P450 3A4 system. *In vitro*, nefazodone have been shown to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore when both medicines are co-administered, an increase in plasma concentrations of nifedipine cannot be excluded. If co-administered, blood pressure should be monitored and if necessary, a dose reduction of BIO NIFEDIPINE XL be considered.

Quinupristin/dalfopristin

Simultaneous administration of quinupristin/dalfopristin and BIO NIFEDIPINE XL may lead to

increased plasma concentrations of BIO NIFEDIPINE XL. Upon co-administration of both medicines, the blood pressure should be monitored and if necessary, a reduction of the BIO NIFEDIPINE XL dose considered.

Valproic acid

As valproic acid has been shown to increase in plasma concentrations of the structurally similar calcium channel nimodipine due to enzyme inhibition, an increase in plasma concentration of nifedipine and hence an increase in efficacy cannot be excluded.

Cimetidine

As cimetidine inhibits the cytochrome P450 3A4 system, the co-administration of cimetidine with BIO NIFEDIPINE XL can increase the bioavailability of BIO NIFEDIPINE XL.

Cisapride

Concomitant administration of cisapride and BIO NIFEDIPINE XL can lead to increased BIO NIFEDIPINE XL concentrations; a dosage reduction may be required.

Phenytoin:

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

Carbamazepine and phenobarbitone

As carbamazepine and phenobarbitone have been shown to reduce the plasma concentrations of the

structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in plasma concentrations of nifedipine and hence a decrease in efficacy cannot be excluded.

Effects of BIO NIFEDIPINE XL on other medicines

When administered concomitantly, BIO NIFEDIPINE XL may increase the blood pressure lowering effect of anti-hypertensives such as:

- diuretics
- β-Blockers
- ACE-Inhibitors
- angiotensin receptor blockers
- other calcium channel antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa.

Severe hypotension has been reported in patients receiving BIO NIFEDIPINE XL and β-receptor blockers simultaneously (refer to WARNINGS AND SPECIAL PRECAUTIONS). Caution is advised as administration of these two medicines together can lead to heart failure. The use of any other antihypertensive medication with BIO NIFEDIPINE XL can lead to severe hypotension.

Digoxin

Concomitant administration of BIO NIFEDIPINE XL and digoxin can reduce digoxin clearance and hence an increase in plasma concentrations. The patient should be closely monitored for digoxin overdosage.

Quinidine

When BIO NIFEDIPINE XL and quinidine were administered simultaneously, lowered quinidine or, after discontinuation of BIO NIFEDIPINE XL, a distinct increase in plasma concentrations of quinidine

has been observed. For this reason, when BIO NIFEDIPINE XL is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose is recommended.

Increased plasma concentrations of BIO NIFEDIPINE XL have been reported upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of BIO NIFEDIPINE XL. Therefore, the blood pressure should be carefully monitored if quinidine is added to an existing therapy with BIO NIFEDIPINE XL. If necessary, the dose of BIO NIFEDIPINE XL should be decreased.

Tacrolimus

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

Diltiazem

Diltiazem reduces the hepatic metabolism of BIO NIFEDIPINE XL. The co-administration of these medicines should be carefully monitored and a reduction in dosage for both medicines may be required.

Barium

BIO NIFEDIPINE XL can interfere with the results of barium contrast X-ray procedures (see section 4.4).

Medicine – food interactions

Grapefruit juice

Grapefruit juice inhibits the metabolism of BIO NIFEDIPINE XL. Administration of BIO NIFEDIPINE XL together with grapefruit juice thus results in elevated plasma concentrations of BIO NIFEDIPINE XL due to a decreased first pass metabolism in the gastrointestinal tract. As a consequence, the blood

pressure lowering effect may be increased (see section 4.4).

Other forms of interactions

BIO NIFEDIPINE XL may cause falsely increase spectrophotometric values of urinary vanillylmandelic acid. However, measurement with HPLC is unaffected.

4.6 Fertility, pregnancy and lactation

BIO NIFEDIPINE XL is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

Co-administration of BIO NIFEDIPINE XL with I.V. magnesium sulfate may cause an excessive fall in blood pressure which could harm both mother and fetus.

Breastfeeding

Mothers taking BIO NIFEDIPINE XL should not breastfeed their babies, and mothers breastfeeding their babies should not take BIO NIFEDIPINE XL as nifedipine passes into breast milk.

Fertility

Preclinical and animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects when administered during any stage of pregnancy, and decreased neonatal survival after birth. Only a life-threatening hypertensive crisis of the mother in the late trimester of pregnancy, who is not responding to any other treatment, may override this contraindication.

4.7 Effects on ability to drive and use machines

BIO NIFEDIPINE XL can impair the ability to drive or to operate machinery, especially during the start of treatment, changing the dose and in combination with alcohol. The intensity of the reaction to BIO NIFEDIPINE XL varies from patient to patient.

4.8 Undesirable effects

Frequently experienced side effects, associated with its vasodilator action are dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia and palpitations.

Blood and lymphatic system disorders

Less frequent: Leucopenia, purpura.

Immune system disorders

Less frequent: Hypersensitivity reaction, chills, fever, allergic reactions (incl. pruritus, urticaria, rash), angioedema (incl. larynx oedema*).

Metabolism and nutrition disorders

Less frequent: Anorexia, weight loss.

Psychiatric disorders

Less frequent: Anxiety, sleep disorder.

Nervous system disorders

Frequent: Headache.

Less frequent: Dizziness, insomnia, nervousness, paraesthesia, dysaesthesia, somnolence, vertigo, tremor, migraine.

Eye disorders

Frequent: Eye pain.

Less frequent: Abnormal vision, eye disorder, blurred vision.

Cardiac disorders

Less frequent: Chest pain, tachycardia, palpitations, chest pain substernal, angina pectoris (excl. unstable).

Vascular disorders

Frequent: Peripheral oedema, vasodilatation.

Less frequent: Hypotension, postural hypotension, syncope, cardiovascular disorder, face oedema.

Respiratory, thoracic and mediastinal disorders

Less frequent: Epistaxis, nasal congestion.

Gastrointestinal disorders

Frequent: Constipation.

Less frequent: Abdominal pain, diarrhoea, dyspepsia, flatulence and nausea, dry mouth, eructation, gastrointestinal disorder, gingivitis, gingival hyperplasia, oesophagitis, gum disorders, gastro-oesophageal reflux.

Hepato-biliary disorders

Less frequent: Abnormal liver function test, increased GGT (gamma-glutamyl transpeptidase), increased transaminases.

Skin and subcutaneous tissue disorders

Less frequent: Pruritus, rash, maculopapular rash, pustular rash, sweating, urticaria, vesiculobullous rash, exfoliative dermatitis, erythema, palpable purpura.

Musculoskeletal and connective tissue disorders

Less frequent: Leg cramps and pain, arthralgia, joint swelling, myalgia, muscle cramps.

Renal and urinary disorders

Less frequent: Nocturia, polyuria, dysuria, urinary frequency.

Reproductive system and breast disorders

Less frequent: Erectile dysfunction.

General disorders and administration site conditions

Frequent: Malaise, asthenia, oedema.

Less frequent: Pain.

* may result in life-threatening outcome

Post-marketing experience

System Organ Class	**Frequency unknown**
Blood and lymphatic system disorders	Agranulocytosis
Immune system disorders	Anaphylactic/anaphylactoid reaction
Endocrine disorders	Gynaecomastia
Metabolism and nutrition disorders	Hyperglycaemia
Nervous system disorders	Hypoaesthesia
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Bezoar dysphagia Intestinal obstruction Intestinal ulcer Vomiting Gastroesophageal sphincter insufficiency
Hepato-biliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis Photosensitivity allergic reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO NIFEDIPINE XL is important. It allows continued monitoring of the benefit/risk balance of BIO NIFEDIPINE XL. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

If the following symptoms are observed in time, the first therapeutic measure to be considered is gastric lavage with added medical charcoal: flushing, headache, sever hypotension, increase or decrease in heart rate, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema and unconsciousness to the point of coma.

Treatment is symptomatic and supportive. No specific antidote is available.

Hypotension (due to cardiogenic shock and arterial vasodilatation): slow IV calcium; 10 – 20 ml of a 10 % calcium gluconate solution. This can be repeated if necessary. If the result is insufficient, vasoconstricting sympathomimetics such as dopamine or noradrenaline can additionally be administered. The dosage of these agents is determined by the effect obtained. Additional volume must be administered with caution because of the danger of overloading the heart.

Bradycardia: β-sympathomimetics and in life-threatening bradycardiac disturbances of heart rhythm, temporary pacemaker therapy is advised.

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

5. PHARMACOLOGICAL PROPERTIES

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 channel blocker, 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 vascular resistance and an increase in peripheral blood flow. Ca2+-channel blockers are useful in low-renin hypertension. Nifedipine dilates submaximally 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

General characteristics

The mechanism of release of nifedipine from BIO NIFEDIPINE XL is by membrane-controlled, osmotic push-pull process; nifedipine is released at a zero-order rate over 24 hours. The rate of delivery is not influenced by gastrointestinal pH or motility. After swallowing the excipients of the tablet remain intact and are eliminated as an insoluble shell in the faeces.

Absorption

After oral administration nifedipine is almost completely absorbed.

Administration in the presence of food does not influence the availability of nifedipine.

Distribution

Nifedipine is about 95 % bound to plasma protein (albumin).

Biotransformation

Nifedipine is metabolised in the gut wall and liver, primarily by oxidative processes. The metabolites are predominantly eliminated by the kidneys, with approximately 5 – 15 % being excreted via the bile in the faeces.

Elimination

The terminal half-life of nifedipine osmotic push-pull release process does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption.

Hepatic impairment

The elimination half-life is distinctly prolonged and the total clearance is reduced in patients with impaired hepatic function. BIO NIFEDIPINE XL should not be administered to these patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose acetate

Colloidal silicon dioxide

Ferric oxide red (colourant)

Hypromellose

Magnesium stearate

Opacode black (colourant)

Opadry brown (consisting of hypromellose, iron oxide red (colourant), iron oxide yellow (colourant), polyethylene glycol and titanium dioxide (colourant))

Polyethylene glycol

Polyethylene oxide

Potassium chloride

Sodium chloride.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the blister strips in the outer carton and keep the carton closed until required for use.

6.5 Nature and contents of container

Plain aluminium (no external colour), transparent and colourless PVC blister strips; 10 tablets per strip.

Three (3) blister strips are packed into an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

BIOTECH LABORATORIES (PTY) LTD

Block K West, Central Park,

400 16th Road, Halfway House

Midrand

1685

8. REGISTRATION NUMBERS

BIO NIFEDIPINE XL 30: 43/7.1/0558

BIO NIFEDIPINE XL 60: 43/7.1/0559

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2012

10. DATE OF REVISION OF THE TEXT

21 January 2022

NAMIBIA REGISTRATION ONLY:

NS2 BIO NIFEDIPINE XL 30

Reg. No.: 13/7.1/0228

(Act No. 13 of 2003).

NS2 BIO NIFEDIPINE XL 60

Reg. No.: 13/7.1/0229

(Act No. 13 of 2003).