Professional information for BIO-NIFEDIPINE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BIO-NIFEDIPINE 5 capsules, soft

BIO-NIFEDIPINE 10 capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BIO-NIFEDIPINE 5: Each capsule contains 5 mg nifedipine.

BIO-NIFEDIPINE 10: Each capsule contains 10 mg nifedipine.

Sugar free.

Excipients with known effect:

Contains sweetener: Sodium saccharin.

BIO-NIFEDIPINE 5: Each capsule contains 0,10 mg sodium saccharin.

BIO-NIFEDIPINE 10: Each capsule contains 0,20 mg sodium saccharin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft.

BIO-NIFEDIPINE 5: Light orange one piece oval capsule with glossy surface and median sealing line.

BIO-NIFEDIPINE 10: Light orange one piece oblong capsule with glossy surface and median sealing line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of angina pectoris including variant angina.

4.2 Posology and method of administration

Posology

The initial oral dose is 10 mg, given three times daily. This dosage should then be titrated over a period of 7 to 14 days to control symptoms of angina.

The usual dose is 10 to 20 mg three times daily.

For a more rapid onset of action, the capsule should be bitten and the contents allowed to remain in the mouth for a short time.

Special populations

Elderly patients

The recommended dosage in elderly patients or those on concomitant medicine is 5 mg taken three times daily.

Children and adolescents

The use of BIO-NIFEDIPINE in children is contraindicated (see section 4.3).

4.3 Contraindications

- Hypersensitivity to nifedipine or dihydropyridines, because of the theoretical risk of cross-reactivity, calcium antagonists, or to any of the excipients listed in section 6.1.
- The safety of BIO-NIFEDIPINE in pregnancy and lactation has not been established (see section 4.6).
- The safety of BIO-NIFEDIPINE in malignant hypertension has not been established.
- BIO-NIFEDIPINE has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients (see section 4.4).
- BIO-NIFEDIPINE should not be administered concomitantly with rifampicin, since effective

plasma levels of BIO-NIFEDIPINE may not be achieved owing to enzyme induction (see section 4.5).

BIO-NIFEDIPINE should not be used:

- In patients with hepatic impairment.
- In patients with a history of gastrointestinal obstruction, oesophageal obstruction or any degree of decreased lumen diameter of the gastrointestinal tract.
- In patients with inflammatory bowel disease.
- In cardiogenic shock and in patients who have suffered a myocardial infarction in the previous 2 to 4 weeks.
- In unstable angina or to treat an angina attack in chronic stable angina.
- In clinically significant aortic stenosis. BIO-NIFEDIPINE may increase the risk of developing heart failure.
- For secondary prevention of myocardial infarction.
- In children.
- In patients with Kock pouch (ileostomy after proctocolectomy).

4.4 Special warnings and precautions for use

BIO-NIFEDIPINE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal. Any such withdrawal should be a gradual reduction of the dose of beta-blocker, preferably over 8 – 10 days.

BIO-NIFEDIPINE may be used in combination with beta-blockers and other antihypertensive medicines, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. BIO-NIFEDIPINE will not prevent possible rebound effects after cessation of other antihypertensive therapy.

BIO-NIFEDIPINE should be used with caution in patients with heart failure or whose cardiac reserve is poor, since deterioration of heart failure may occur.

In patients who experience ischaemic pain following administration of BIO-NIFEDIPINE, therapy should be discontinued. Although a “steal” effect has not been demonstrated, patients experiencing this effect should discontinue BIO-NIFEDIPINE therapy.

At doses higher than those recommended, there is some concern about increased mortality and morbidity in the treatment of ischaemic heart disease, in particular after myocardial infarction (see section 4.3).

BIO-NIFEDIPINE should be used with caution in patients with hypotension as it may induce an exaggerated fall in blood pressure and reflex tachycardia, which can cause cardiovascular complications such as myocardial and cerebrovascular ischaemia. Blood pressure should be monitored carefully during initiation of therapy and during upward titration of dosage, especially if patients are on antihypertensive therapy.

As with other vasoactive medicines, angina pectoris may occur with BIO-NIFEDIPINE, especially at the start of the treatment.

In patients suffering from angina pectoris, an increase in frequency, duration and severity of angina pectoris attacks may occur, especially at the start of treatment.
Sudden withdrawal of BIO-NIFEDIPINE might be associated with an exacerbation of angina.

Myocardial infarction has occurred, although it is not possible to distinguish this from the natural course of the underlying disease.

BIO-NIFEDIPINE should not be used during pregnancy.

Careful monitoring of blood pressure must be performed when administering nifedipine with

intravenous magnesium sulphate, owing to the potential for an excessive fall in blood pressure, which could harm both mother and fetus (see section 4.6).

BIO-NIFEDIPINE is not recommended 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).

The use of BIO-NIFEDIPINE in diabetic patients may require adjustment of their control.

BIO-NIFEDIPINE has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients (see section 4.3).

In single cases, obstructive symptoms have been described without a known history of gastrointestinal disorders. When doing barium contrast X-ray, BIO-NIFEDIPINE may cause false positive effects (e.g. filling defects interpreted as polyp).

Excipient warnings

BIO-BIFEDIPINE contains Sunset Yellow (C.I. no. 15985) as colourant, which may cause allergic reactions.

BIO-NIFEDIPINE contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on BIO-NIFEDIPINE

BIO-NIFEDIPINE is extensively metabolised by the cytochrome P450-enzyme system, located both in the intestinal mucosa and in the liver. Medicines that are known to either inhibit or induce this enzyme system may alter the first pass metabolism or clearance of BIO-NIFEDIPINE.

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

Rifampicin

Rifampicin strongly induces the CYP3A4 system. Upon co-administration with rifampicin, the bioavailability of BIO-NIFEDIPINE is distinctly reduced and its efficacy weakened. The use of BIO-NIFEDIPINE in combination with rifampicin is therefore contraindicated (see section 4.3).

Medicines that are known inhibitors of the CYP3A4 system may lead to increased BIO-NIFEDIPINE plasma concentrations. Therefore, upon co-administration of known inhibitors of the CYP3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the BIO-NIFEDIPINE dose considered (see sections 4.2 and 4.4).

Medicines increasing BIO-NIFEDIPINE exposure:

- Macrolide antibiotics (e.g. erythromycin).
- Anti-HIV protease inhibitors (e.g. ritonavir).
- Azole antimycotics (e.g. ketoconazole).
- The antidepressants nefazodone and fluoxetine.
- Quinupristin/dalfopristin.
- Cisapride.
- Valproic acid.
- Cimetidine.
- Diltiazem.

Upon co-administration of inducers of the CYP3A4 system, the clinical response to BIO-NIFEDIPINE should be monitored and, if necessary, an increase in the BIO-NIFEDIPINE dose considered. If the dose of BIO-NIFEDIPINE is increased during co-administration of both medicines, a reduction of the BIO-NIFEDIPINE dose should be considered when the treatment is discontinued.

Medicines decreasing BIO-NIFEDIPINE exposure:

- Rifampicin (see above).
- Phenytoin.
- Carbamazepine.
- Phenobarbital.

Effects of BIO-NIFEDIPINE on other medicines

BIO-NIFEDIPINE may enhance the antihypertensive effects of other antihypertensive medicines, such as:

- Diuretics.
- Beta-blockers.
- Angiotensin-converting enzyme (ACE) inhibitors.
- Angiotensin II receptor antagonists.
- Other calcium antagonists.
- Alpha-adrenergic blocking medicines.
- Phosphodiesterase type 5 (PDE5) inhibitors.
- Alpha-methyldopa.

Enhanced antihypertensive effects may also be seen with concomitant use of medicines such as antipsychotics that cause hypotension.

When BIO-NIFEDIPINE is administered simultaneously with beta-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases (see section 4.4).

BIO-NIFEDIPINE may modify insulin and glucose responses. Therefore, diabetic patients may need to adjust their antidiabetic treatment (see section 4.4).

Digoxin

Concomitant administration of BIO-NIFEDIPINE has increased plasma digoxin levels, due to reduced digoxin clearance. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

Quinidine

Co-administration of BIO-NIFEDIPINE with quinidine may lower plasma quinidine levels, and after discontinuation of BIO-NIFEDIPINE, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when BIO-NIFEDIPINE is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of BIO-NIFEDIPINE should be decreased.

Tacrolimus

Tacrolimus is metabolised via the CYP3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine, as contained in BIO-NIFEDIPINE, may be reduced in individual cases. Upon coadministration of both medicines, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Medicine food interactions

Grapefruit juice inhibits the CYP3A4 system. Therefore, the concomitant administration of BIO-NIFEDIPINE and grapefruit juice results in elevated plasma concentrations and prolonged action of BIO-NIFEDIPINE, due to a decreased first pass metabolism or reduced clearance. Consequently, the blood pressure-lowering effect of BIO-NIFEDIPINE 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 should be avoided while taking BIO-NIFEDIPINE.

Other forms of interaction

BIO-NIFEDIPINE may falsely elevate the spectrophotometric values of urinary vanillylmandelic acid. However, high performance liquid chromatography (HPLC) measurements are unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy

BIO-NIFEDIPINE should not be used during pregnancy (see section 4.4).

In animal studies, nifedipine (as contained in BIO-NIFEDIPINE) has been shown to produce embryotoxicity, fetotoxicity and teratogenicity (see section 5.3).

An increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific medicine effect.

The available information is inadequate to rule out adverse medicine effects on the unborn and newborn child.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine (as contained in BIO-NIFEDIPINE), have been used as a tocolytic medicine during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breastfeeding

BIO-NIFEDIPINE is distributed into the breast milk. The BIO-NIFEDIPINE concentration in the milk is almost comparable with mother serum concentration. It is proposed to delay breastfeeding or milk expression for 3 to 4 hours after medicine administration to decrease the BIO-NIFEDIPINE exposure to the infant (see section 4.4).

Fertility

In single cases of *in vitro* fertilisation, calcium antagonists, such as BIO-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, such as BIO-NIFEDIPINE, should be considered as possible causes.

4.7 Effects on ability to drive and use machines

BIO-NIFEDIPINE may cause side effects such as dizziness, lethargy and visual disturbances, which can affect the ability to drive a vehicle and use machines (see section 4.8). This applies particularly at the start of treatment, when changing medication and in combination with alcohol. Caution is advised before driving a vehicle or operating machines until the effects of BIO-NIFEDIPINE are known.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse effects of BIO-NIFEDIPINE are associated with its vasodilator action and often diminish on continued therapy.

List of adverse reactions

Blood and lymphatic system disorders

Frequency unknown: Agranulocytosis, leucopenia.

Immune system disorders

Less frequent: Allergic reaction, allergic oedema/angioedema (including larynx oedema, which may result in a life-threatening outcome), pruritus, urticaria. There have been reports of rashes (including erythema multiforme), fever and

abnormalities in liver function, including cholestasis, due to hypersensitivity reactions.

Frequency unknown: Anaphylactic/anaphylactoid reaction.

Metabolism and nutrition disorders

Less frequent: Hyperglycaemia.

Psychiatric disorders

Less frequent: Anxiety reactions, sleep disorders.

Nervous system disorders

Frequent: Headache.

Less frequent: Lethargy, nervousness, insomnia, mental depression, tremor, vertigo, migraine, dizziness, paraesthesia/dysaesthesia.

Frequency unknown: Hypoaesthesia, somnolence.

Eye disorders

Less frequent: Eye pain, visual disturbances.

Cardiac disorders

Less frequent: Palpitations and precipitation of angina pain, tachycardia, myocardial infarction.

A paradoxical increase in ischaemic chest pain may occur at the start of treatment.

Vascular disorders

Frequent: Flushing (vasodilatation), oedema (including peripheral oedema).

Less frequent: Hypotension, syncope.

In a few patients, excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

Respiratory, thoracic and mediastinal disorders

Less frequent: Nasal congestion, nosebleed.

Frequency unknown: Dyspnoea, pulmonary oedema (cases have been reported when used as tocolytic during pregnancy (see section 4.6)).

Gastrointestinal disorders

Frequent: Nausea, constipation.

Less frequent: Gastrointestinal and abdominal pain, dyspepsia, flatulence, dry mouth, gingival hyperplasia.

Frequency unknown: Vomiting, gastro-oesophageal sphincter insufficiency.

Hepatobiliary disorders

Less frequent: Transient increase in liver enzymes.

Frequency unknown: Jaundice.

Skin and subcutaneous tissue disorders

Less frequent: Perspiration, erythema.

Frequency unknown: Toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura.

Musculoskeletal and connective tissue disorders

Less frequent: Arthralgia, myalgia, muscle cramps, joint swelling.

Renal and urinary disorders

Less frequent: Increased micturition frequency, polyuria, dysuria.

Reproductive system and breast disorders

Less frequent: Erectile dysfunction, impotence

General disorders and administration site conditions

Frequent: Feeling unwell.

Less frequent: Unspecific pain, chills.

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 vasodilatation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO-NIFEDIPINE is important. It allows continued monitoring of the benefit/risk balance of BIO-NIFEDIPINE. 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

The following symptoms are observed in cases of severe BIO-NIFEDIPINE overdose:

- disturbances of consciousness to the point of coma,
- a drop in blood pressure,
- tachycardia,
- bradycardia,
- hyperglycaemia,
- metabolic acidosis,

- hypoxia,
- cardiogenic shock with pulmonary oedema.

Treatment

As far as treatment is concerned, elimination of BIO-NIFEDIPINE and the restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. The benefit of gastric decontamination is uncertain.

1) Activated charcoal should be considered if the patient presents within 1 hour of ingestion of a potentially toxic amount.
2) Alternatively, consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.
3) Asymptomatic patients should be observed for at least 4 hours after ingestion.

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

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium, with electrocardiogram (ECG) monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics, such as dopamine or noradrenaline, should be administered.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Nifedipine is a specific and potent calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the myocardium and the smooth muscle cells of the peripheral resistance vessels and coronary arteries. Its main action is to relax arterial smooth muscle both in the coronary and peripheral circulation.

In angina pectoris, BIO-NIFEDIPINE relaxes peripheral arteries thereby reducing the load on the left ventricle. Additionally, nifedipine dilates submaximally both clear and pre-stenotic, stenotic and post-stenotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

BIO-NIFEDIPINE reduces the frequency of painful attacks and ischaemic ECG changes, irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Nifedipine causes a reduction in blood pressure such that the percentage lowering is directly related to its initial height. In normotensive individuals, nifedipine has little or no effect on blood pressure.

In Raynaud's syndrome, nifedipine can prevent or reduce the occurrence of digital vasospasm.

5.2 Pharmacokinetic properties

Absorption

After oral administration, nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations is 45 – 56 % owing to a first pass effect. Maximum plasma and serum concentrations are reached at 30 to 60 minutes. Simultaneous food intake leads to delayed, but not reduced absorption.

Distribution

Nifedipine is about 95 % bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

Biotransformation

After oral administration, nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites, predominantly via the kidneys and about 5 – 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0,1 %) in the urine.

Elimination

The terminal elimination half-life is 1,7 to 3,4 hours. No accumulation of the substance after the usual dose was reported during long-term treatment. In cases of impaired kidney function, no substantial changes have been detected in comparison with healthy volunteers.
In a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced. As a result, AUC and C_{max} of nifedipine increased, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine have not been investigated in patients with severe hepatic impairment.

5.3 Preclinical safety data

Reproduction toxicology

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including

digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved. However, all of the doses associated with the teratogenic, embryotoxic or fetotoxic effects in animals were maternally toxic and were several times the maximum dose for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Peppermint oil

Polyethylene glycol 400

Polysorbate 80

Purified water

Sodium saccharin.

Capsule shell:

Gelatine

Glycerine

Sunset Yellow dye (C.I. no. 15985)

Titanium dioxide (C.I. no. 77891).

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 light.

6.5 Nature and contents of container

PVC and foil blister strips in cartons containing 84, 100 and 250 capsules or 100 or 250 capsules in polypropylene containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road

Randjespark

Midrand 1685

South Africa

8. REGISTRATION NUMBERS

BIO-NIFEDIPINE 5: X/7.1/102

BIO-NIFEDIPINE 10: X/7.1/103

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 August 1990

10. DATE OF REVISION OF THE TEXT

22 May 2022