SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Fidocare XL 30 prolonged-release tablets

Fidocare XL 60 prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

Excipients with known effect

Sodium chloride:

Each 30 mg tablet contains 9,52 mg of sodium (see section 4.4).

Each 60 mg tablet contains 19,04 mg of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

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

Fidocare 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

The recommended initial dose is one 30 mg tablet 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 days period so that the response to each dose level can be assessed before proceeding to higher doses.

Special populations

Patients with renal impairment

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

Patients with hepatic impairment

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

Elderly patients

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

Paediatric population

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

Method of administration

Oral use.

The tablets should be swallowed whole with a glass of fluid; under no circumstances should they be bitten, chewed or broken up. Grapefruit juice is to be avoided.

The tablets should be taken at approximately 24 hour intervals, i.e. at the same time each day, preferably during the morning. Fidocare XL may be taken irrespective of meal times.

4.3 Contraindications

Fidocare XL should not be administered to patients with known hypersensitivity to nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients listed in sections 4.4 and 6.1.

Fidocare XL should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

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

Fidocare XL should not be used for secondary prevention of myocardial infarction.

Owing to the duration of action of the formulation, Fidocare XL should not be administered to patients with hepatic impairment.

Fidocare XL should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.

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

Fidocare XL is contraindicated in patients with inflammatory bowel disease or Crohn's disease.

Fidocare XL should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.5).

Fidocare XL is contraindicated in pregnancy and during breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

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

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

Fidocare XL is contraindicated during pregnancy (see section 4.3 and 4.6).

Careful monitoring of blood pressure must be exercised when administering Fidocare XL with I.V. 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.

Fidocare XL 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).

Fidocare XL is contraindicated in patients with hepatic impairment (see section 4.2 and 4.3).

Fidocare XL 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.

Fidocare XL will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Fidocare XL should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Diabetic patients taking Fidocare XL may require adjustment of their control.

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see section 4.5).

Medicines, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example (see section 4.5):

- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole antimycotics (e.g., ketoconazole)
- the antidepressants, nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acids
- cimetidine
- diltiazem

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

As the outer membrane of the Fidocare XL tablet is not digested, what appears to be the complete tablet 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 Fidocare XL to patients, as obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention.

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

A false positive effect may be experienced when performing a barium contrast X-ray (e.g. filling defects interpreted as polyp).

For use in special populations see section 4.2.

Grapefruit juice inhibits the metabolism of nifedipine. 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 Fidocare XL (see section 4.5).

Safety of Fidocare XL 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.

Although a "coronary steal" effect has not been demonstrated, Fidocare XL therapy should be discontinued in patients experiencing this effect.

Fidocare XL should not be switched once a patient has been stabilised, without appropriate monitoring.

Excipients

Fidocare XL 30 contains 9,52 mg of sodium and Fidocare XL 60 contains 19,04 mg of sodium.

Increasing the daily dose to 90 mg Fidocare XL 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

Medicines that affect nifedipine

Fidocare 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 (see section 4.4).

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

Rifampicin

Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of Fidocare XL in combination with rifampicin is therefore contraindicated (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 Fidocare XL 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.

Medicines increasing nifedipine exposure:

- *macrolide antibiotics (e.g., erythromycin)*
- *anti-HIV protease inhibitors (e.g., ritonavir)*

- *azole anti-mycotics (e.g., ketoconazole)*
- *fluoxetine*
- *nefazodone*
- *quinupristin/dalfopristin*
- *cisapride*
- *valproic acid*
- *cimetidine*
- *diltiazem*

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

Medicines decreasing nifedipine exposure:

- *rifampicin (see above)*
- *phenytoin*
- *carbamazepine*
- *phenobarbitone*

Effects of Fidocare XL on other medicines

Fidocare XL may exacerbate the blood pressure lowering effect of concomitantly applied antihypertensive, such as:

- diuretics
- β-Blockers
- ACE-Inhibitors

- angiotensin receptor blockers
- other calcium channel antagonists
- α-adrenergic blocking medicines
- PDE5 inhibitors
- α-methyldopa.

When Fidocare XL is administered simultaneously with ß-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin

The simultaneous administration of Fidocare XL and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin over dosage and, if necessary, the glycoside dose should be reduced.

Quinidine

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

Tacrolimus

Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with Fidocare XL may be reduced in individual cases. Upon co-administration 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 cytochrome P450 3A4 system. Administration of Fidocare XL together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of Fidocare XL 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 Fidocare XL (see section 4.2).

Other forms of interaction

Fidocare XL may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy

Fidocare XL 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 Fidocare XL with I.V. magnesium sulphate may cause an excessive fall in blood pressure which could harm both mother and foetus.

Breastfeeding

Fidocare XL 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 Fidocare XL, 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

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, are listed below:

System Organ Class (MedDRA)	**Frequency unknown**
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 Fidocare XL is important. It allows continued monitoring of the benefit/risk balance of Fidocare XL. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 Fidocare XL 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

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 is a 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. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Fidocare XL is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.

In hypertension, the main action of nifedipine is to cause peripheral vasodilatation and thus reduce peripheral resistance.

Nifedipine administered once-daily provides 24-hour control of raised blood pressure.

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

In angina, Fidocare XL reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load. Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium. Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

In a multi-national, randomised, double-blind, prospective study involving 6 321 hypertensive patients with at least one additional risk factor followed over 3 to 4,8 years, Fidocare XL 30 and 60 (nifedipine GITS) were shown to reduce blood pressure to a comparable degree as a standard diuretic combination.

Paediatric population

Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with different formulations in different dosages. Antihypertensive effects of nifedipine have been demonstrated but dose recommendations, long term safety and effect on cardiovascular outcome remain unestablished.

Paediatric dosing forms are lacking.

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. The bioavailability of the 20 mg tablet is proportional to that of the 30 mg tablet.

5.2 Pharmacokinetic properties

General characteristics

Fidocare XL tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0 – 24 hour plasma concentration versus time profiles at steady state are plateau-like, rendering the Fidocare XL tablet appropriate for once-a day administration.

The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45 – 56 % owing to a first pass effect. At steady-state, the bioavailability of Fidocare XL tablets range from 68 – 86 % relative to nifedipine capsules.

Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

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 eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5 – 15 % being excreted via the bile in the faeces. Non-metabolised nifedipine can be detected only in traces (below 0,1 %) in the urine.

Elimination

The terminal elimination half-life is 1,7 to 3,4 h in conventional formulations (nifedipine capsules). The terminal half-life following Fidocare XL administration does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of the last dose the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

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. Fidocare XL should not be administered in 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

4 years for 30 mg tablets and

3 years for 60 mg tablets.

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

10 tablets in an aluminium PVC blister; 3 such blisters with product insert into a carton.

30 tablets per carton.

6.6 Special precautions for disposal and other handling

No additional information.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

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8. REGISTRATION NUMBERS

Fidocare XL 30: 50/7.1/0504

Fidocare XL 60: 50/7.1/0505

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 July 2020

10. DATE OF REVISION OF THE TEXT

22 July 2025