SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE MEDICINAL PRODUCT

M & B Nifedipine XL Tablet 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	NAME OF THE INGREDIENTS	STANDARD	QTY. REQD.	OVERAGES (%)	ACTUAL QTY. USED
1.	Nifedipine	BP	15.30 kg	5.00%	16.07 kg
2.	Colloidal Anhydrous Silica	BP	0.51 kg	--	0.51 kg
3.	Colour Opadry White	IHS	2.04 kg	--	2.04 kg
4.	Colour Quinoline Yellow (Lake)	IHS	0.20 kg	--	0.20 kg
5.	Polyethylene Glycol 6000	BP	0.10 kg		0.10 kg
6.	Dichloromethane	BP	23.00 Ltr.		23.00 Ltr.
7.	Starch 1500 (Pregelatinised)	BP	25.50 kg		25.50 kg
8.	Hypromellose	BP	20.60 kg		20.60 kg
9.	Isopropyl Alcohol	BP	33.130 Ltr.	--	33.130 Ltr.
10.	Lactose (Spray Dried)	BP	25.500 kg		25.500 kg
11.	Magnesium Stearate	BP	1.02 kg	--	1.02 kg
12.	Microcrystalline Cellulose	BP	10.00 kg	--	10.00 kg

3. PHARMACEUTICAL FORM

Tablet

4. Clinical particulars

4.1 Therapeutic indications

The Nifedipine Retard Tablet is indicated for:

- the treatment of all grades of hypertension
- the prophylaxis of chronic stable angina pectoris, either as monotherapy or in combination with a beta-blocker.

4.2 Posology and method of administration

Posology

In severe hypertension, 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.

For the prophylaxis of angina pectoris, the recommended initial dose is one 30 mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90 mg once-daily.

Prophylactic antianginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Nifedipine XL. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30 mg Nifedipine XL once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see section E).

Duration of treatment

Treatment may be continued indefinitely.

Additional information on special populations

Paediatric population

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

Elderly

Based on pharmacokinetic data for Nifedipine XL Tablet no dose adaptation in elderly people above 65 years is necessary.

Renal impairment

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

Method of administration

Oral use.

The tablets should be swallowed whole with a glass of water, either with or without food. The tablets should be taken at approximately 24-hour intervals, i.e. at the same time each day, preferably during the morning. Nifedipine XL Tablet must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

4.3 Contraindications

Nifedipine XL Tablet 30mg is contraindicated:

- in patients with a known hypersensitivity to the drug or other constituents of the tablets

- in patients with a known hypersensitivity to other dihydropyridines calcium antagonists, because of the theoretical risk of cross-reactivity

- in women who are or may become pregnant, are capable of child bearing or to nursing mothers

- in patients with clinically significant aortic stenosis, in cardiogenic shock or unstable angina or for the treatment of acute attacks of angina

- in patients with inflammatory bowel disease, Crohn's disease or with a history of gastrointestinal obstruction, oesophageal obstruction or with decreased diameter of the gastrointestinal lumen

- in patients with hepatic impairment

- for secondary prevention of myocardial infarction or during or within one month of a myocardial infarction

The safety of nifedipine extended release tablets has not been established in patients with malignant hypertension.

4.4 Special warnings and precautions for use

Nifedipine XL tablet 30mg 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).

Nifedipine XL tablet 30mg should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine XL tablet should be reserved for women with severe hypertension who are unresponsive to standard therapy.

Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus.

Nifedipine XL tablet is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known.

In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Nifedipine XL tablet may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind Nifedipine extended release tablets will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Nifedipine XL tablet 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 Nifedipine XL tablet 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. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of Nifedipine.

Drugs, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:

- 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 acid

- Cimetidine

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

As the outer membrane of the Nifedipine 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 Nifedipine XL tablet 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.

4.5 Interaction with other medicinal products and other forms of interaction

The following drugs are predicted to increase the exposure to Nifedipine:

- Antiarrhythmics
- Antifungals, Azoles
- Aprepitant
- Diltiazem
- Cobicistat
- Crizotinib
- Grapefruit juice
- HIV-protease inhibitiors
- Idelalisib
- Imatinib
- Macrolides
- Netupitant
- Nilotinib

The following drugs are predicted to decrease the exposure to Nifedipine:

- Antiepileptics
- Bosentan
- Efavirenz
- Enzalutamide
- Rifampicin
- St john's wort

4.6 Pregnancy and Lactation

Pregnancy

Nifedipine XL should not be used during pregnancy unless the clinical condition of the woman requires treatment with Nifedipine.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity.

There are no adequate and well-controlled studies in pregnant women.

From the clinical evidence available a specific prenatal risk has not been identified, although 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 drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy requires a very careful individual risk-benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

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

Breast-feeding

Nifedipine is excreted in the breast milk. The Nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant.

Fertility

In single reports of in vitro fertilisation, calcium antagonists like nifedipine have been associated with biochemical alterations in the head of the spermatozoa that may impair sperm function. Calcium antagonists like nifedipine should be considered as possible causes in those men who are repeatedly unsuccessful in fathering a child by in vitro fertilization and where no other explanation can be found.

4.7 Effects on ability to drive and use machines

Reactions to Nifedipine XL Tablet 30 mg may vary in intensity in patients, especially at the onset of therapy, on changing medication or when combined with alcohol. Therefore, the patient should be warned of the possible effects and advised not to drive or operate machinery, if affected.

4.8 Side-effects

Common or very common

Constipation, malaise, oedema, vasodilation.

Uncommon

Allergic oedema, angioedema, anxiety, chills, dry mouth, epistaxis, gastrointestinal discomfort, hypotension, joint disorders, laryngeal oedema, migraine, muscle complaints, nasal congestion, pain, sleep disorder, syncope, tremor, urinary disorders, vertigo, visual impairment.

Rare or very rare

Sensation abnormal

Frequency not known

Agranulocytosis, angina pectoris, chest pain, drowsiness, dyspnea, eye pain, hyperglycemia, jaundice, leucopenia, photo allergic reaction, pulmonary oedema, toxic epidermal necrolysis.

4.9 Overdose

Symptoms

There are few reports of nifedipine overdose and the symptoms are not necessarily dose-related. The most likely manifestations of overdose are severe hypotension due to vasodilatation, tachycardia or bradycardia.

The metabolic disturbances may include hyperglycemia, metabolic acidosis and hypo- or hyperkalemia. The cardiac effects, which may occur, include heart block, AV dissociation and a systole and cardiogenic shock with pulmonary oedema.

Other toxic effects include drowsiness, dizziness, confusion, nausea, vomiting, lethargy, flushing, hypoxia, unconsciousness and coma.

Management

In the treatment of overdose it is important to restore stable cardiovascular conditions as soon as possible and achieve total elimination of nifedipine.

Gastric lavage and charcoal instillation may be of assistance if the patient is found early after the overdose. Gastric lavage may be necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

To prevent the subsequent absorption of nifedipine, elimination must be complete, including from the small intestine.

Activated charcoal should be given in 4 hourly doses of 25g for adults and 10g for children. The blood pressure, central arterial pressure, ECG, electrolytes, pulmonary wedge pressure and urea should be carefully monitored.

Placing the patient in the supine position with the feet raised and the use of plasma expanders, as appropriate, should treat the hypotension resulting from cardiogenic shock and arterial vasodilatation. If these measures are ineffective, hypotension may be treated with 10ml to 20ml of 10% calcium gluconate, administered intravenously over a period of 5 to 10 minutes. If ineffective, the therapy can be continued, with ECG monitoring.

Also, beta-sympathomimetics may be given eg. 0.2mg of isoprenaline by slow intravenous or 5µg per minute as a continuous infusion. If the blood pressure response is inadequate with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The patient's response should determine the dosage of these drugs.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Anatomical Therapeutic Chemical (ATC) code: C08C A05

Selective calcium channel blocker (dihydropyridine derivative), with mainly vascular effects.

Nifedipine is a dihydropyridine and is a specific and potent antagonist of calcium influx through the slow channel of the cell membrane of cardiac and smooth muscle cells, both in coronary and peripheral circulation.

The antihypertensive effects of nifedipine are achieved by causing peripheral vasodilatation resulting in a reduction in peripheral resistance. Nifedipine administered once daily provides twenty-four hours control of elevated blood pressure. Nifedipine reduces blood pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect.

Nifedipine produces its effects in the treatment of angina by reducing peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume and causing a decrease in after-load. Also, nifedipine submaximally dilates clear and atherosclerosis coronary arteries to protect the heart against coronary artery spasm and improve perfusion to the ischaemic myocardium. Nifedipine decreases the frequency of painful attacks and the ischaemic ECG changes regardless of the relative contribution from coronary artery spasm or atheroschlerosis.

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.

5.2 Pharmacokinetic properties

General Characteristics

Nifedipine XL tablet is formulated as extend release products. They are designed to control the release of nifedipine over twenty-four hours so that a clinical effect is achieved when the tablets are swallowed, once a day.

The pharmacokinetic profile is characterized by low peak-trough fluctuation. Over twenty-four hours plasma concentration versus time profiles at steady state are plateau-like, rendering the Nifedipine XL suitable for once daily administration.

Absorption

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. However, due to extensive hepatic first pass metabolism in the liver, the resultant bioavailability lies between 45% and 68%. The absorption rate is slightly changed when the tablets are taken after ingesting food but the extent of drug availability is not affected.

Distribution

Nifedipine is about 95% bound to plasma proteins.

Metabolism

Nifedipine is almost completely metabolised in the liver by oxidative and hydrolytic processes.

Elimination

The elimination half-life is 2 to 5 hours. About 70% to 80% of the administered dose of nifedipine is excreted via the kidneys, mostly as its active metabolites. The rest (5 % to 15 %) is excreted via the bile in the faeces. The non-metabolised drug substance is only found in traces (less than 1.0 %) in the urine.

Characteristics in Patients

Patients with Renal Impairment

There are no significant differences in the pharmacokinetics of nifedipine in patients with renal impairment and in healthy subjects. Therefore, dosage adjustments should not be required for patients with impaired renal function.

Patients with Hepatic Impairment

Nifedipine is primarily metabolised in the liver. The elimination half-life is markedly prolonged and there is a reduction in total clearance. Therefore, owing to the duration of action, nifedipine should not be administered to patients with reduced hepatic function.

5.3 Preclinical safety data

The LD_{50} values (in mg per Kg) determined when nifedipine was given orally and intravenously to different animal species, are reported below:

Animal Species	*Oral*	*Intravenous*
Mouse	454 (401 - 572) *	4.2 (3.8 - 4.6) *
Rat	1022 (950 - 1087) *	15.5 (13.7 - 17.5) *
Rabbit	250 - 500	2 - 3
Cat	~ 100	0.5 - 8
Dog	> 250	2 - 3

* 95% confidence interval

Subacute & Subchronic Toxicity Studies (in Rats and Dogs)

Nifedipine doses of up to 50mg per Kg in rats and 100mg per kg in dogs p.o were tolerated without any damage when administered orally over periods of thirteen and four weeks, respectively.

Nifedipine doses of 2.5mg per kg in rats and 0.1mg per kg in dogs were tolerated without any damage when administered intravenously over periods of three weeks and six days, respectively.

Chronic Toxicity Studies (in Rats and Dogs)

Nifedipine doses of up to and including 100mg per kg in dog's p.o were tolerated without any damage when administered orally up to one year.

In rats, toxic effect occurred at nifedipine concentrations above 100ppm in the feed (about 5mg to

7mg per kg body weight).

Carcinogenic Studies (in Rats)

Studies in rats over two years produced no evidence of carcinogenic effects caused by nifedipine.

Reproductive Studies (in Rats, Mice & Rabbits)

Studies in rats, mice and rabbits maternally toxic doses of nifedipine induced some teratogenic and embryotoxic effects.

Mutagenic Studies

In vivo and in vitro studies showed that nifedipine has no mutagenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Anhydrous Silica	BP
Colour Opadry White	IHS
Colour Quinolone Yellow (Lake)	IHS
Polyethylene Glycol 6000	BP
Dichloromethane	BP
Starch 1500 (Pregelatinised)	BP
Hypromellose	BP
Isopropyl Alcohol	BP
Lactose (Spray Dried)	BP
Magnesium Stearate	BP
Microcrystalline Cellulose	BP

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

Shelf life of the medicinal product as package for sale is 27 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

10 tablets are packed in a blister strip. 3 such strips along with a leaflet are packed in a printed carton. 50 such cartons are shrink packed. 10 such shrink pack are packed in a outer box.

6.6 Special precautions for disposal <and other handling>

Not Applicable

7. APPLICANT/MANUFACTURER

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