SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE MEDICINAL PRODUCT

M & B Nifedipine Retard Tablet 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	NAME OF THE INGREDIENTS	STANDARD	QTY. REQD.	OVERAGES (%)	ACTUAL QTY. USED
A.	**Blending**				
1.	Nifedipine	BP	10.20 kg	5.00 %	10.71 kg
2.	Pregelatinised Starch	BP	25.50 kg	--	25.50 kg
3.	Hypromellose (Methocel K-100)	BP	20.60 kg	--	20.60 kg
4.	Lactose (Spray Dried)	BP	30.86 kg	--	30.86 kg
5.	Microcrystalline Cellulose	BP	10.00 kg	--	10.00 kg
6.	Magnesium Stearate	BP	1.02 kg	--	1.02 kg
7.	Colloidal Anhydrous Silica	BP	0.51 kg	--	0.51 kg
8.	Opadry White (Non-Aquous)	IHS	1.50 kg	--	1.50 kg
9.	Isopropyl Alcohol	BP	38.27 Lts.	--	38.27 Lts.
10.	Dichloromethane	BP	25.55 Lts.	--	25.55 Lts.
11.	Polyethylene Glycol-6000	IP	0.383 kg	--	0.383 kg
12.	Colour Iron Oxide Red	IHS	0.37 kg	--	0.37 kg
13.	Colour Iron Oxide Yellow	IHS	0.089 kg	--	0.089 kg

3. PHARMACEUTICAL FORM

Tablet

Brown coloured round, biconvex film coated retard release tablets imprints of “MBN” on one side and “CR” on other side.

4. Clinical particulars

4.1 Therapeutic indications

Nifedipine Retard Tablets 20mg are indicated for the following:

(i) Hypertension

(ii) The prophylaxis of chronic stable angina pectoris

4.2 Posology and method of administration

Posology

It is recommended that these tablets are swallowed with a glass of water. These tablets must be swallowed whole and not broken or chewed.

Adults: The recommended dose is one tablet (20 mg) every 12 hours. The dosage may be increased up to 40 mg every 12 hours to achieve the desired effect.

Paediatric population

The safety and efficacy of nifedipine in children under the age 18 years have not been established. Currently available data for the use of nifedipine in hypertension.

Elderly

There are no special dosage requirements for the elderly, however, the pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Patients with hepatic dysfunction must be carefully monitored when treatment is commenced as Nifedipine Retard Tablet is primarily metabolised in the liver. If hepatic function is impaired, the dosage requirements of nifedipine should be established before use of Nifedipine Retard Tablet.

Dosage adjustments should not be required for patients with renal impairment.

Treatment with Nifedipine Retard may be continued long term.

Method of Administration

Oral Administration.

4.3 Contraindications

Acute attacks of angina, cardiogenic shock, significant aortic stenosis, unstable angina, within 1 month of myocardial infarction

4.4 Special warnings and precautions for use

Nifedipine should be used with caution in patients with severe hypotension and in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Nifedipine may enhance the effects of other antihypertensive agents such as beta-blockers (although this combination is well tolerated) resulting in postural hypotension. Nifedipine will not

prevent the occurrence of rebound effects following the discontinuation of other antihypertensive agents.

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 pressure less than 90 mm Hg).

Cardiac ischaemic pain has been reported to have occurred in some patients within 1-4 hours of receiving nifedipine. In such cases treatment should be discontinued.

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

Caution should be exercised when Nifedipine Retard Tablet is given to diabetic patients as nifedipine may impair glucose tolerance, and may require adjustment of diabetic therapy.

In patients with malignant hypertension and hypovolaemia who are on dialysis, a significant 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 that 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.

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

Nifedipine Retard Tablet is not recommended for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of oral absorption of small amounts of nifedipine are not known.

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

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

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

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.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent 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.

Breast-feeding

Nifedipine passes into 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 cases of *in vitro* fertilization, 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* fertilization, 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

Nifedipine Retard Tablet 20mg may make you feel sick, dizzy, extremely tired or suffer headaches. If any of these symptoms are experienced, do not derived or operate machinery or pursue any activity in which full attention is required.

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

This may be associated with severe hypotension, tachycardia or bradycardia and unconsciousness although there are few reports and the symptoms are not necessarily dose-related.

The metabolic disturbances which can occur include hyperglycaemia and metabolic acidosis. The cardiac effects which may occur include heart block, AV dissociation and asystole and cardiogenic shock with pulmonary oedema.

Other effects include drowsiness, dizziness, confusion, nausea, vomiting, lethargy, flushing, hypoxia, disturbances of consciousness to the point of coma.

Treatment-

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. After oral ingestion thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Particularly in the cases of intoxication with slow release nifedipine formulations such as Nifedipine Retard, elimination must be 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. Consider activated charcoal (50 g for adults, 1 g/kg for children) 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. Consider further doses of activated charcoal (alternatively ipecacuanha) every 4 hours, if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulphate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion.

Haemodialysis serves no purpose as 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 (10-20ml of a 10% calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained.Bradycardiac heart rhythm disturbances may be treated symptomatically with beta-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm, temporaray pacemaker therapy can be advisable. It has also been reported that the use of metaraminol combined with calcium salts has been beneficial. Care should be exercised to avoid cardiac overload when administering additional fluids or volume.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

ATC Code: C08

Nifedipine is a dihydropyridine and is a potent antagonist of calcium influx through the slow channel of the cell membrane of cardiac and smooth muscle cells. Nifedipine also binds to intracellular calcium binding proteins.

Calcium is normally released from the sarcoplasmic reticulum intracellularly and this combined with the influx of extracellular calcium results in enhanced binding calcium to calmodulin. Calcium channel blockers such as Nifedipine act as arteriolar dilators by inhibiting this calcium entry into the channel. The effects are more pronounced on vascular smooth muscle because depolarisation of cardiac muscle cells is dependent on both sodium ion influx and calcium ion influx and also nifedipine has little effect on the rate of recovery of the slow calcium channel.

Nifedipine is known to be an effective and relatively well tolerated treatment for angina and mild to severe hypertension.

The antihypertensive effects of nifedipine are achieved by causing peripheral vasodilatation resulting in a reduction in peripheral resistance. Nifedipine reduces blood pressure in hypertension but has little or no effect in normotensive individuals.

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.

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

Nifedipine is rapidly and almost completely absorbed from the gastro-intestinal tract after oral administration, however due to extensive hepatic first pass metabolism, the resultant bioavailability lies between 45% and 75%. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

The terminal elimination half-life is 1.7 to 3.4 h in conventional formulations (nifedipine capsules). The terminal half-life following Nifedipine retard 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

Nifedipine is about 92%-98% bound to plasma proteins (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

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.

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. Owing to the duration of action of the formulation, nifedipine retard should not be administered in these patients.

Mean data from the comparative bioavailability study is presented below:

Pharmacokinetic parameters measured after 6 days at steady state (mean N=24)	Nifedipine Retard Tablet
C_{MAX}	58.5ng/ml
T½ ß	17.30 hours
AUC $_{0\text{-}48\ hours}$	413 ng/ml/hour
$AUC_{0\text{-}INF}$	517 ng/ml/hour
T_{MAX}	2.21 hours

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Following acute oral and intravenous administration of nifedipine in various animal species, the following LD_{50} (mg/kg) values were obtained:

Mouse:	Oral: 494 (421-572)*;	i.v.: 4.2 (3.8-4.6)*.
Rat:	Oral: 1022 (950-1087)*;	i.v.: 15.5 (13.7-17.5)*.
Rabbit	Oral: 250-500;	i.v.: 2-3.
Cat:	Oral: ~ 100;	i.v.: 0.5-8.
Dog:	Oral: > 250;	i.v.: 2-3.
* 95% confidence interval.		

In subacute and subchronic toxicity studies in rats and dogs, nifedipine was tolerated without damage at doses of up to 50 mg/kg (rats) and 100 mg/kg (dogs) p.o. over periods of thirteen and four weeks, respectively. Following intravenous administration, dogs tolerated up to 0.1 mg/kg nifedipine for six days without damage. Rats tolerated daily intravenous administration of 2.5 mg/kg nifedipine over a period of three weeks without damage.

In chronic toxicity studies in dogs with treatment lasting up to one year, nifedipine was tolerated without damage at doses up to and including 100 mg/kg p.o. In rats, toxic effects occurred at concentrations above 100 ppm in the feed (approximately 5-7 mg/kg bodyweight).

In a carcinogenicity study in rats (two years), there was no evidence of a carcinogenic effect of nifedipine.

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 foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal 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 foetotoxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans.

In *in vitro* and *in vivo* tests, nifedipine has not been associated with mutagenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Starch	BP
Hypromellose (Methocel K-100)	BP
Lactose (Spray Dried)	BP
Microcrystalline Cellulose	BP
Magnesium Stearate	BP
Colloidal Anhydrous Silica	BP
Opadry White (Non-Aquous)	IHS
Isopropyl Alcohol	BP
Dichloromethane	BP
Polyethylene Glycol 6000	IP
Colour Iron Oxide Red	IHS
Colour Iron Oxide Yellow	IHS

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 aluminum blister strip. 5 such strips along with a leaflet are packed in a printed carton. 10 such cartons are shrink packed together. 50 such shrink packs are packed in a outer box, which is duly labeled and strapped. (25000 tablets)

6.6 Special precautions for disposal <and other handling>

Not Applicable.

7. MANUFACTURER

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