SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

NIFEDIPINE EXTENDED RELEASE TABLET USP 20 MG

2. Qualitative and quantitative composition

Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tablet (mg)	Actual Qty/batch (kg)	Function
Dry Mixing					
1.	Nifedipine USP*	20.000	20.000	2.000	L-type calcium channel blocker
2.	Hypromellose (K100-LV Premium) BP	-	24.000	2.400	Matrixing Agent
3.	Hypromellose (K4M) BP	-	24.000	2.400	Matrixing Agent
4.	Lactose BP**	-	53.000	5.300	Diluent
5.	Pregelatinised Starch BP	-	15.000	1.500	Dry Binder
Blending & Lubrication					
6.	Colloidal anhydrous silica BP	-	2.000	0.200	Glidant
7.	Magnesium Stearate BP	-	2.000	0.200	Lubricant
Total Weight of Uncoated Tablet			**140.00 mg**	**14.000 kg**	

3. Pharmaceutical forms

Oral Extended Release Uncoated Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

For the treatment of mild to moderate hypertension.

For 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 mild to moderate hypertension, the recommended initial dose is one 20 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.

Patients in whom hypertension or anginal symptoms are controlled on Adalat capsules or Adalat retard may be safely switched to Nifedipine Extended Release Tablet. Prophylactic anti-anginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Nifedipine Extended Release Tablet. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30 mg Nifedipine Extended Release Tablet 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.

Duration of treatment:
Treatment may be continued indefinitely.

Additional information on special populations

Paediatric population:
The safety and efficacy of Nifedipine Extended Release Tablet in children below 18 years has not been established.Currently available data for the use of nifedipine in hypertension.

Elderly:
Based on pharmacokinetic data for Nifedipine Extended Release 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 Extended Release Tablet tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Nifedipine Extended Release Tablet should not be taken with grapefruit juice.

4.3 Contraindications

Nifedipine Extended Release Tablet should not be administered to patients with known hypersensitivity to the active substance, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.

Nifedipine Extended Release Tablet 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.

Nifedipine Extended Release Tablet should not be used for the treatment of acute attacks of angina.

The safety of Nifedipine Extended Release Tablet in malignant hypertension has not been established.

Nifedipine Extended Release Tablet should not be used for secondary prevention of myocardial infarction.

Owing to the duration of action of the formulation, Nifedipine Extended Release Tablet should not be administered to patients with hepatic impairment.

Nifedipine Extended Release Tablet 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.

Nifedipine Extended Release Tablet must not be used in patients with a Kock pouch (ileostomy after proctocolectomy).

Nifedipine Extended Release Tablet is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.

Nifedipine Extended Release Tablet should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

4.4 Special warning and precaution for use

Nifedipine Extended Release Tablet 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).

Nifedipine Extended Release Tablet should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine Extended Release 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. For further information regarding use in pregnancy.

Nifedipine Extended Release 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 Extended Release 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 Tablet will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Nifedipine Extended Release 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 Extended Release 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 Extended Release Tablet 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 Extended Release 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

Drugs that affect nifedipine:
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs 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 nifedipine together with the following drugs:

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 nifedipine in combination with rifampicin is therefore contraindicated.

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 nifedipine dose considered. In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

Drugs 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 nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Drugs decreasing nifedipine exposure:

- rifampicin (see above)
- phenytoin
- carbamazepine
- phenobarbital

Effects of nifedipine on other drugs:

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives.

When nifedipine 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 nifedipine 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 overdosage and, if necessary, the glycoside dose should be reduced.

Quinidine:
Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when 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 nifedipine should be decreased.

Tacrolimus:
Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug food interactions:

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine 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 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 is therefore to be avoided while taking nifedipine.

Other forms of interaction:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Nifedipine 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 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 breast-feeding 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 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 the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n =

2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

The frequencies of ADRs reported with nifedipine-containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under “Not known”.

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Not Known**
Blood and Lymphatic System Disorders				Agranulocytosis Leucopenia
Immune System Disorders		Allergic reaction Allergic oedema/angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric Disorders		Anxiety reactions Sleep disorders		
Metabolism and Nutrition Disorders				Hyperglycaemia
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/Dysaesthesia	Hypoaesthesia Somnolence
Eye Disorders		Visual disturbances		Eye pain
Cardiac Disorders		Tachycardia Palpitations		Chest pain (Angina pectoris)
Vascular Disorders	Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnoea Pulmonary oedema**
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting Gastroesophageal sphincter insufficiency