BELCO PHARMA
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Haryana (INDIA)

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1 The denomination of the Generic drug and the International Non-Proprietary Name of Active(s) principles.

TRADE NAME : NIFEDIPINE RETARD

INN : Nifedipine Retard Tablets

1.3.1.2 Pharmaceutical Form

Tablet

1.3.1.3 Strength

20 mg/Tablet

1.3.1.4 Presentation

10× 5 Tablets

1.3.1.5 Route of Administration

Oral

1.3.1.6 Qualitative-Quantitative composition in Active & Excipients

Batch Size: 5.1 Lac.

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
B. Lubrication					
6.	Magnesium Stearate	BP	1.02 kg	--	1.02 kg
7.	Colloidal Anhydrous Silica	BP	0.51 kg	--	0.51 kg
C. Coating					
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

1.3.1.7 Clinical Particulars

(A) Therapeutic Indications:

Nifedipine Retard tablets are indicated for the following:

(i) Hypertension

(ii) The prophylaxis of chronic stable angina pectoris

(B) Posology and 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 is primarily metabolised in the liver. If hepatic function is impaired, the dosage requirements of nifedipine should be established before use of Nifedipine Retard.

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.

(C) Contraindications: Hypersensitivity to nifedipine, any of the excipients or other dihydropyridines because of the theoretical risk of cross reactivity.

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

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

The safety of nifedipine in malignant hypertension has not been established.

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

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

Nifedipine 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 must not be used in patients with a Kock pouch (ileostomy after Proctocolectomy).

Nifedipine is contra-indicated in patients with inflammatory bowel disease or Crohn's disease

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

(D) Special Warning 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 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 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

(E) 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 the following weak to moderate 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.

Macrolide antibiotics (e.g., erythromycin)

No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded.

Azithromycin, although structurally related to the class of macrolide antibiotics is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors (e.g., ritonavir)

A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. In addition, drugs of this class have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded.

Azole anti-mycotics (e.g., ketoconazole)

A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded.

Fluoxetine

A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit in vitro the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded.

Nefazodone

A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded.

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine.

Valproic acid

No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme

inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded.

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect.

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.

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

Cytochrome P450 3A4 system inducing anti-epileptic drugs, such as phenytoin, carbamazepine and phenobarbitone

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of 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 with phenytoin is discontinued.

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy cannot be excluded.

Effects of nifedipine on other drugs

Blood pressure lowering drugs

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

- diuretics,

- β-blockers,

- ACE-inhibitors,

- Angiotensin 1(AT1) receptor- antagonists,

- other calcium antagonists,

- α-adrenergic blocking agents,

- PDE5 inhibitors,

- α-methyldopa

When 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. Withdrawal of any previous antihypertensive agents should be gradual as nifedipine will not compensate for any possible rebound effects.

Quinidine

It is reported that serum quinidine levels have been shown to be reduced when it is used in combination with nifedipine 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. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine.

Therefore, the blood pressure should be carefully monitored, if quinidine is added to an existing therapy with nifedipine. 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.

Concurrent administration of nifedipine along with theophylline and phenytoin will lead to increased plasma levels of theophylline and phenytoin, and the enhanced effect of non-polarising muscle relaxants such as tubocurarine.

Digoxin

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and therefore bring about an increase in the plasma concentrations of digoxin level. . The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Drug food interactions

Grapefruit juice

As with other dihydropyridines, nifedipine should not be taken with grapefruit juice because bioavailability is increased.

Grapefruit juice inhibits the cytochrome P450 3A4 system, 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.

(F) Fertility, Pregnancy and Lactation:

Pregnancy

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.

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* 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.

(G) Effects on ability to drive and use machine:

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.

Nausea, headaches, lethargy and dizziness have been reported to occur and therefore the patient should be warned of these possible effects.

(H) 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%). ADRs derived from post marketing reports, and for which a frequency could not be estimated are printed in ***bold italic***.

Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to <0.1%	Frequency Not Known
Blood and Lymphatic System Disorders			
			Agranulocytosis ***Leucopenia***
Immune System Disorder			
	Allergic reaction Allergic oedema / angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	***Anaphylactic/ anaphylactoid reaction***
Metabolism and Nutrition Disorders			
			Hyperglycaemia
Psychiatric Disorders			
	Anxiety reactions Sleep disorders		
Nervous System Disorders			
Headache	Migraine Vertigo Dizziness Tremor	Dysaesthesia, paraesthesia, lethargy	***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			
	Nasal congestion Nosebleed		***Dyspnoea*** ***Pulmonary oedema*****
Gastrointestinal Disorders			
Constipation	Gastrointestinal and abdominal pain Dyspepsia Flatulence Dry mouth, nausea	Gingival hyperplasia	***Vomiting, Bezoar*** ***Dysphagia,*** ***Intestinal obstruction,*** ***Intestinal ulcer,*** ***Gastroesophageal sphincter insufficiency***
Hepatobiliary Disorders			
	Transient increase in liver enzymes		***Jaundice***
Skin and Subcutaneous Tissue Disorders			
	Erythema		***Toxic Epidermal Necrolysis*** ***Photosensitivity allergic reaction*** ***Palpable purpura***
Musculoskeletal and Connective Tissue Disorders			
	Muscle cramps Joint swelling		***Myalgia, Arthralgia***
Renal and Urinary Disorders			
	Dysuria, Polyuria	Increased frequency of micturition	
Reproductive System and Breast Disorders			
	Erectile dysfunction		
General Disorders and Administration Site Conditions			
Feeling unwell	Unspecific pain Chills		

* = may result in life-threatening outcome

**cases have been reported when used as tocolytic during pregnancy

Exacerbation of angina pectoris may occur frequently at the start of treatment with short acting formulations of nifedipine. The occurrence of myocardial infarction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

Gingival hyperplasia and, in older men, gynaecomastia have been reported but these are usually reversible on drug withdrawal. Hypersensitivity reactions such as skin rashes and abnormalities of liver function have occurred. These symptoms disappear upon discontinuation of nifedipine.

In dialysis patients with malignant hypertension and hypovolaemia, a distinct fall in blood pressure can occur as a result of vasodilation.

(I) 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.

1.3.1.8 Pharmacological Properties:

(A) Pharmacodynamic 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.

(B) 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.

The dosage schedule for a standard capsule formulation of nifedipine is 10 mg three times daily leading to a maximum of 20 mg three times daily. The nifedipine tablet is designed as a modified release product to provide a twice daily dosing of 20 mg which can be increased to 40 mg twice daily if necessary.

Adalat Retard is a modified release formulation currently available on the UK market. A comparative bioavailability study has been carried out comparing this preparation with Nifedipine Retard. The results of the study are provided below and demonstrate that these two preparations are bioequivalent.

Mean data from the comparative bioavailability study is presented below:

Pharmacokinetic parameters measured after 6 days at steady state (mean N=24)	Adalat Retard Tablet	Nifedipine Retard Tablet
C_{MAX}	58.7ng/ml	58.5ng/ml
T½ ß	13.31 hours	17.30 hours
AUC $_{0\text{-}48\ hours}$	407 ng/ml/hour	413 ng/ml/hour
$AUC_{0\text{-}INF}$	480 ng/ml/hour	517 ng/ml/hour
T_{MAX}	2.00 hours	2.21 hours

(C) 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.

1.3.1.9 Pharmaceutical Particulars:

(A) 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

(B) Incompatibility:

Not Applicable.

(C) Shelf Life:

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

(D) Special Precautions for Storage:

Store below 30°C.

(E) 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)