

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1 NAME OF THE MEDICINAL PRODUCT**

Nidef 60 mg Prolonged Release Tablets

Nifedipine Morningside 60 mg Prolonged Release Tablets

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each prolonged release tablet contains 60 mg nifedipine.

Each tablet contains a 10% overage of nifedipine to deliver the label claim.

For the full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

Prolonged Release Tablets

Pink coloured, film coated circular biconvex tablet, having orifice on one side and plain on other side and imprinted with 'X' on any one side.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

For the treatment of all grades of 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. 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.

Patients in whom hypertension or anginal symptoms are controlled on Nifedipine capsules or Nifedipine modified release tablets may be safely switched to Nifedipine prolonged release tablets.

Prophylactic anti-anginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Nifedipine prolonged release tablets.

Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30 mg Nifedipine prolonged release tablets 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 4.5).

#### *Duration of treatment*

Treatment may be continued indefinitely.

#### ***Additional information on special populations***

##### *Paediatric population*

The safety and efficacy of Nidef / Nifedipine Prolonged Released Tablets in children below 18 years has not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1.

*Elderly* Based on pharmacokinetics data for nifedipine 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 (see Section 5.2).

##### *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. Nidef / Nifedipine Prolonged Released Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Nidef / Nifedipine Prolonged Released Tablets should not be taken with grapefruit juice (see Section 4.5).

### **4.3 Contraindications**

Nidef / Nifedipine Prolonged Released Tablets are contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the

theoretical risk of cross-reactivity. They should also not be used in cases of known hypersensitivity to any of the excipients listed in section 4.4 and 6.1.

They should not be used in nursing mothers and women who are or who may become pregnant (see section 4.6).

Nidef / Nifedipine Prolonged Released Tablets should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction. They should not be used in patients in cardiogenic shock.

Nidef / Nifedipine Prolonged Released Tablet should not be used for the treatment of acute attacks of angina, or in patients who have had ischaemic pain following its administration previously.

The safety of Nidef / Nifedipine Prolonged Released Tablet in malignant hypertension has not been established.

Nidef / Nifedipine Prolonged Released Tablet should not be used for secondary prevention of myocardial infarction.

Nidef / Nifedipine Prolonged Released Tablet should be contraindicated in patients with acute porphyria.

Nidef / Nifedipine Prolonged Released Tablet should not be used in patients with Kock pouch (ileostomy after proctocolectomy).

Nidef / Nifedipine Prolonged Released Tablets should not be administered concomitantly with rifampicin since efficient plasma levels of nifedipine may be achieved owing to enzyme induction (see section 4.5).

As Nidef / Nifedipine Prolonged Released Tablets is a long acting formulation, it should not be administered to patients with hepatic impairment (see section 4.5).

#### **4.4 Special warnings and precautions for use**

Nifedipine should be used with caution in patients who are hypotensive 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).

The use of Nifedipine in diabetic patients may require adjustment of their diabetic therapy.

In dialysis patients with malignant hypertension and irreversible renal failure with hypovolaemia, a significant drop in blood pressure may occur due to the vasodilator effects of nifedipine.

Nifedipine should be used with caution in patients whose cardiac reserve is poor; in patients with heart failure or significantly impaired left ventricular function. Deterioration of heart failure has occasionally been observed with nifedipine.

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

Excessive falls in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see section 4.8).

Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

Since nifedipine has no beta-blocking activity, it gives no protection against the dangers of abrupt withdrawal of beta-blocking drugs. Withdrawal of any previously prescribed betablockers should be gradual, preferably over 8 to 10 days.

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

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 (see section 4.5).

Drugs, which are inhibitors on the cytochrome P450 3A4 system, and therefore lead to increased plasma concentrations of nifedipine are, 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 (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## **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 (see section 4.4).

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 contra-indicated (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 nifedipine dose considered (see section 4.2 and 4.4). 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*
- *H<sub>2</sub>-receptor antagonist (specifically cimetidine)*
- *Other calcium channel blockers (specifically 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.

Increased plasma levels of nifedipine have been reported during concomitant use of alcohol, cyclosporin, ginkgo biloba and ginseng.

Enhanced hypotensive effect of nifedipine may occur with: aldesleukin, alprostadil, anaesthetics, antipsychotics, diuretics, phenothiazides, prazosin and intravenous ionic X-ray contrast medium. Profound hypotension has been reported with nifedipine and intravenous magnesium sulphate in the treatment of pre-eclampsia.

Drugs decreasing nifedipine exposure:

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

Decreased plasma levels of nifedipine have been reported during concomitant use of St John's Wort.

Effects of nifedipine on other drugs

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

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.

*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 level 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 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.

The plasma concentrations of phenytoin, theophylline, non-depolarising muscle relaxants (e.g. tubocurarine) are increased when used in combination with nifedipine.

There is an increased risk of excessive hypotension, bradycardia and heart failure with  $\beta$ -blockers.

Nifedipine may result in increased levels of mizolastine due to inhibition of cytochrome CYP3A4.

Nifedipine may increase the neuromuscular blocking effects of vecuronium.

*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 may be increased. After regular intake of grapefruit juice this 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 nifedipine (see section 4.2).

*Other forms of interaction:*

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

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

Because animal studies show embryotoxicity, and teratogenicity, nifedipine is contraindicated during pregnancy (see section 4.3). Embryotoxicity was noted at 6 to 20 times the maximum recommended dose for nifedipine given to rats, mice and rabbits, and teratogenicity was noted in rabbits given 20 times the maximum recommended dose for nifedipine. There are no adequate well controlled studies in pregnant women.

An increase in perinatal asphyxia, caesarean delivery as well as prematurity and intrauterine growth retardation has been reported, however it is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

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 is excreted in the breast milk, therefore Nidef/ Nifedipine Prolonged Released Tablets are not recommended during lactation (see section 4.3).

### **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. Nifedipine should be considered as possible causes if there is no other explanation for unsuccessful fathering.

## **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 (see section 4.8). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

Dizziness and lethargy are potential undesirable effects. If affected do not attempt to drive or use machinery (see section 4.8).

Excessive falls in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see section 4.8).

## **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%). Most side-effects are consequences of the vasodilatory effects of nifedipine.

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 ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) and rare ( $\geq 1/10,000$  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".

<b>System Organ Class (MedDRA)</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Not Known</b>
Blood and Lymphatic System Disorders				Agranulocytosis Leucopenia
Immune System Disorders		Allergic reaction Allergic oedema/angioedema (incl. larynx oedema <sup>1</sup> )	Pruritus Urticaria Rash	Anaphlactic/anaphylactoid reaction Systemic allergic reactions
Psychiatric Disorders		Anxiety reactions Sleep disorders	Mood changes	Depression
Metabolism and Nutrition Disorders				Hyperglycaemia
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor	Par- /Dysaesthesia	Hypoesthesia Somnolence Lethargy Cerebral ischemia (due to excessive fall in blood pressure)
Eye Disorders		Visual disturbances		Eye pain Transient blindness (due to excessive fall in blood pressure)
Cardiac Disorders		Tachycardia Palpitations		Chest pain (Angina pectoris) Myocardial infarction <sup>2</sup> Myocardial ischemia (due to excessive fall in blood pressure)
Vascular Disorders	Oedema (incl. Peripheral oedema)	Hypotension Syncope		Flushing

<b>System Organ Class (MedDRA)</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Not Known</b>
	Vasodilatation			
Respiratory, Thoracic, and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnoea Pulmonary oedema <sup>*</sup>
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastroesophageal sphincter insufficiency Diarrhoea Dysphagia Intestinal ulcer
Hepatobiliary Disorders		Transient increase in liver enzymes		Jaundice Intra-hepatic cholestasis
Skin and Subcutaneous Tissue Disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura Telangiectasia Erythema multiforme Pemphigoid reaction Exfoliative dermatitis Purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling		Arthralgia Myalgia Worsening of myasthenia gravis
Renal and Urinary Disorders		Polyuria Dysuria		Increased frequency of micturition
Reproductive System and Breast Disorders		Erectile dysfunction		Gynaecomastia (lon-term therapy)
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		Fever

<sup>1</sup> = may result in life-threatening outcome

<sup>2</sup> = 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.

\*\* = cases have been reported when used as tocolytic during pregnancy (see section 4.6)

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 the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

### Symptoms

Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilation, and tachycardia and bradycardia are the most likely manifestations of overdose.

Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo or hyperkalaemia.

Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.

Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia and unconsciousness 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, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Elimination must be as 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.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

3. Consider further doses of activated charcoal 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 and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Activated charcoal should be given in 4-hourly doses of 25g for adults, 10g for children.

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilation should be treated with elevation of the feet and plasma expanders. If these measures are ineffective, hypotension may be treated with 10% calcium gluconate 10 - 20 ml intravenously over 5-10 minutes. If effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, beta-sympathomimetics may be given, e.g. isoprenaline 0.2 mg slowly i.v. or as a continuous infusion of 5 µg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs should be determined by the patient's response.

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

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives, ATC code: C08 CA05

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. Nifedipine Prolonged Released Tablets are 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, nifedipine 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 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, nifedipine 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.

## **5.2 Pharmacokinetic properties**

General characteristics:

Nidef / Nifedipine Prolonged Released Tablets are a sustained release formulation of nifedipine designed to provide less fluctuation and more prolonged nifedipine blood concentrations than standard immediate release preparations.

Nifedipine is highly protein bound. It undergoes hepatic oxidation to inactive metabolites which are excreted in the urine (80%) and faeces (20%).

## **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 LD50 (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 fetuses (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**

*Core*

Polyethylene Oxide

Hydroxy Propyl Methyl Cellulose (E464)

Sodium Chloride

Polyethylene Oxide  
Ferric Oxide (E172)  
Magnesium Stearate (E572)

*Seal coating*

Hypromellose (E464)

*Cellulose acetate coating*

Cellulose Acetate  
Polyethylene Glycol (E1521)  
Dichloromethane  
Methanol

*Film coating*

Hydroxypropyl cellulose (E463)  
Hypromellose (E464)  
Titanium dioxide (E171)  
Talc (E553b)  
Iron oxide red (E172)

*Imprinting Ink*

Shellac (E904)  
Iron Oxide Black (E172)  
Propylene glycol (E1520)

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Store in the original container

**6.5 Nature and contents of container**

PVC/PE/PVDC, Aluminium Blister. Blister packs of 10, 14, 15, 28, 30, 56, 60, 90 and 112 Prolonged Release Tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special precautions

**7 MARKETING AUTHORISATION HOLDER**

Morningside Healthcare Ltd

Unit C, Harcourt Way

Leicester, LE19 1WP, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20117/0229

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/12/2024

**10 DATE OF REVISION OF THE TEXT**

23/12/2024