

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nidef 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

Pink coloured, film coated circular biconvex prolonged release tablets, having orifice on one side and plain on the other 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

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 Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Nidef should not be taken with grapefruit juice (see Section 4.5).

Dosage regimen

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. Other formulations are available to provide a 20 mg prolonged release tablet.

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

Children and adolescents

The safety and efficacy of Nidef 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.

Geriatric patients

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 renal impairment

Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (see Section 5.2).

4.3 Contraindications

Nidef Tablets must not be used in cases of known hypersensitivity to nifedipine or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients listed in section 6.1.

Nidef Tablets must not be used in cases of cardiovascular shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

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

The safety of Nidef Tablet in malignant hypertension has not been established.

Nidef tablet should not be used for secondary prevention of myocardial infarction.

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

Nidef 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.

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

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

Nidef Tablets must not be used in combination with rifampicin because no efficient plasma levels of nifedipine may be obtained due to enzyme induction (see section 4.5).

4.4 Special warnings and precautions for use

Nidef 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 pressure less than 90 mm HG), in cases of manifest heart failure and in the case of severe aortic stenosis.

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 (see section 4.6).

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 to the infant are not known (see section 4.6).

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

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

Nidef Tablets 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 Nidef Tablets may require adjustment of their control.

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

As with other non-deformable material care should be used when administering Nidef Tablets in patients with pre-existing severe gastrointestinal narrowing because 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.

When doing barium contrast X-ray, Nidef Tablets may cause false positive effects (e.g. filling defects interpreted as polyp).

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

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 known inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, e.g.:

- 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.

For use in special populations see section 4.2.

As the outer membrane of the tablet may not be 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 Nidef tablets to patients, as obstructive symptoms may occur. Bezoars may occur in very rare cases and may require surgical intervention.

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 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 (see section 4.2). 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)

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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

Quinupristin / Dalfopristin

Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (see section 4.4).

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 (see section 4.4).

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (see section 4.4).

Further studies

Cisapride

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

Diltiazem

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.

Drugs decreasing nifedipine exposure:

- rifampicin (see above)
- phenytoin
- carbamazepine

- phenobarbital

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 β -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 plasma concentrations of digoxin. 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.

Quinidine

When nifedipine and quinidine have been administered simultaneously, lowered plasma quinidine levels or, after discontinuation of nifedipine, a distinct increase in plasma concentrations of quinidine has been observed in individual cases. For this reason, 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 coadministration 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 has been shown to be metabolised via the cytochrome P450 3A4 system. Data recently 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.

Drug-food interactions:

Grapefruit juice

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 falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is 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. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.4).

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

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.

In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity (see section 5.3).

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 has been reported. 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. 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 (see section 4.4).

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

Reactions to the drug, which vary in intensity from individual to individual, can 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 ($\geq 1/100$ 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".

| 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 | Hypoesthesia 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** |

| System Organ Class (MedDRA) | Common | Uncommon | Rare | Not Known |
|--|----------------|---|----------------------|---|
| Gastrointestinal Disorders | Constipation | Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth | Gingival hyperplasia | Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting 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 | | Arthralgia Myalgia |
| Renal and Urinary Disorders | | Polyuria Dysuria | | |
| 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**
(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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardia, bradycardia, heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Management of Overdose

As far as treatment is concerned, elimination of the active substance 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 cases of intoxication with slow-release products like nifedipine CR 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).

Bradycardiac heart rhythm disturbances may be treated symptomatically with atropine β -sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10 - 20 ml of a 10 % calcium gluconate solution administered slowly i.v. and repeated if necessary over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. 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.

Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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. Nidef 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.

Pharmacodynamic effects

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 prolonged release tablets reduce 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.

Clinical efficacy and safety

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 prolonged release tablets 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 Tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nidef Tablets are appropriate for once-a-day administration.

The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45–56% owing to a first pass effect. At steady-state, the bioavailability of Nifedipine prolonged release tablets ranges from 68-86% relative to Nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

Distribution

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

Biotransformation

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.

Elimination

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

Characteristics in patients:

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 prolonged release tablets should not be administered in these patients.

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 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

Core

Polyethylene Oxide

Hydroxy Propyl Methyl Cellulose (E463)

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)

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

115 Narborough Road

Leicester

LE3 0PA

UK

8 MARKETING AUTHORISATION NUMBER(S)

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