

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nifedipine Capsules 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 5 mg Nifedipine

Excipient with known effect : Sunset Yellow (E110)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orange oval, soft gelatin capsules with a clear liquid fill material printed G and NE 5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prophylaxis of chronic stable angina pectoris, the treatment of Raynaud's phenomenon and hypertension.

For patients suffering from essential hypertension or chronic stable angina pectoris treated with fast release forms of nifedipine, a dose dependent increase in the risk of cardiovascular complications (e.g. myocardial infarction) and mortality may occur. Because of this, nifedipine capsules should only be used for the treatment of patients with essential hypertension or chronic stable angina pectoris if no other treatment is appropriate.

4.2 Posology and method of administration

Posology

The capsules should be taken orally with a little water, either with or without food. The recommended starting dose is 5mg every 8 hours with subsequent titration of dose according to response. The dose can be increased to 20mg every 8 hours.

Co-administration with cytochrome P450 3A4 inhibitors or inducers may result in increased or reduced serum concentrations of nifedipine. The dose of nifedipine may require adjustment, or an alternative to nifedipine treatment may be necessary.

Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored. Dose reduction may be necessary in severe liver impairment.

Patients with renal impairment should not require adjustment of dosage.

Treatment may be continued indefinitely.

Dosage in the elderly

The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance dose of nifedipine may be required compared to younger patients.

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 are described in section 5.1.

4.3 Contraindications

Nifedipine Capsules should not be administered to 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 women who are or who may become pregnant (see section 4.6).

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

Nifedipine Capsules 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 nifedipine in malignant hypertension has not been established.

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

Nifedipine capsules are contra-indicated in patients with acute porphyria.

Nifedipine capsules should not be used in patients with Kock pouch (ileostomy after proctocolectomy).

Nifedipine Capsules should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (section 4.5).

4.4 Special warnings and precautions for use

Nifedipine should be used with caution in patients who are hypotensive (severe hypotension with systolic blood pressure less than 90 mm Hg).

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

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.

Excessive falls in blood pressure may result in transient blindness. If affected the patient should 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.

Nifedipine is not a beta-blocker and therefore 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-blockers and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension and/or cardiac failure must be borne in mind. Nifedipine will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Nifedipine capsules is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see Section 4.6).

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 enzyme 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 that are known inhibitors of the cytochrome P450 3A4 system, 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).

Nifedipine capsules contain Sunset yellow (E110) which may cause hypersensitivity reactions.

For use in special populations see section 4.2.

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 contraindicated (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 Sections 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*
- *cimetidine*
- *diltiazem*

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered.

If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

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 also 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 levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma

concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon coadministration 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 β -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 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 (see Section 4.2).

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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.

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 breast milk, therefore Nifedipine capsules are not recommended during lactation (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.

Nifedipine should be considered as a possible cause 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 post marketing 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 Leukopenia
Immune system disorders		Allergic reaction Allergic oedema / angioedema (incl. larynx oedema ¹)	Pruritus Urticaria Rash	Anaphylactic/ 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 ² Myocardial ischemia (due to excessive fall in blood pressure)
Vascular disorders	Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		Flushing
Respiratory, thoracic, and mediastinal disorders		Nosebleed Nasal congestion		Dyspnea Pulmonary oedema*
Gastrointestinal disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence	Gingival hyperplasia	Vomiting Gastroesophageal sphincter insufficiency Diarrhoea

		Dry mouth		
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 (long-term therapy)
General disorders and administration site conditions	Feeling unwell	Unspecific pain Chills		Fever

¹ = may result in life-threatening outcome.

² = 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.

4.9 Overdose

Symptoms

Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilation, and tachycardia or 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, unconsciousness and 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. Activated charcoal (50g for adults, 1g/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).

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 the 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 5µg/min.

If an insufficient increase in blood pressure is achieved with calcium vasoconstricting sympathomimetics such as dopamine or noradrenaline should be 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 vasculareffect, dihydropyridine derivatives; ATC Code: C08CA05

Nifedipine is a specific and potent 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. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. In hypertension, the main action of Nifedipine capsules is to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina, Nifedipine capsules 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 ischaemic ECG changes, irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Nifedipine causes a reduction in blood pressure such that the percentage lowering is directly related to its initial height. In normotensive individuals, nifedipine has little or no effect on blood pressure.

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

Absorption

After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations is 45 – 56 % owing to a first pass effect. Maximum plasma and serum concentrations are reached at 30 to 60 minutes. Simultaneous food intake leads to delayed, but not reduced absorption.

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 metabolized in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites predominantly via the kidneys and about 5 – 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1 %) in the urine.

Elimination

The terminal elimination half-life is 1.7 to 3.4 hours. No accumulation of the substance after the usual dose was reported during long-term treatment. In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers.

In a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and Cmax of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see Section 4.4).

5.3 Preclinical safety data

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

Reproduction toxicology

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 maximum dose for humans. (see Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene glycol 400,
Propylene glycol,
Purified water,
Peppermint oil,
Saccharin sodium.

Shell ingredients:

Gelatin,
Glycerol,
Water,
Andrisorb,
Sunset yellow E110,
Titanium dioxide E171.

Printing ink: Monogramming Ink S-1-18086 White

Ingredients:

Shellac Glaze (Modified),
Titanium Dioxide,
Isopropyl Alcohol,
N-Butyl Alcohol

Propylene Glycol.

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light. Store below 25°C.

6.5 Nature and contents of container

PVC/PVdC (285µm)/aluminium foil (25µm) blister strips in a cardboard container.

Pack sizes: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250, 500.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No specific instructions for disposal/handling.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0311

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04th March 1998

10 DATE OF REVISION OF THE TEXT

27/04/2023