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

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 should not be administered to patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross-reactivity or to any of the excipients listed in section 6.1.

Nifedipine 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 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.

Nifedipine 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 is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be gradual reduction of the dose of beta-blocker preferably over 8-10 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 should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

At doses higher than those recommended, there is some concern about increased mortality and morbidity in the treatment of ischaemic heart disease, in particular after myocardial infarction.

Treatment with short-acting nifedipine may induce an exaggerated fall in blood pressure and reflex tachycardia which can cause cardiovascular complications such as myocardial and cerebrovascular ischaemia.

As with other vasoactive substances, angina pectoris may very rarely occur (data from spontaneous reports) with immediate release nifedipine, especially at the start of the treatment. Data from clinical studies confirm that the occurrence of angina pectoris attacks is uncommon.

In patients suffering from angina pectoris, an increase in frequency, duration and severity of angina pectoris attacks may occur, especially at the start of treatment.

Myocardial infarction has occurred, although it is not possible to distinguish this from the natural course of the underlying disease.

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).

Caution should be exercised in patients with severe hypotension (systolic pressure less than 90 mmHg) as there is a risk of further decrease in blood pressure.

The use of nifedipine in diabetic patients may require adjustment of their control.

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

Careful monitoring of blood pressure must be performed when administering nifedipine with intravenous magnesium sulphate, owing to the potential for an excessive fall in blood pressure, which could harm both mother and foetus (For further information regarding use in pregnancy, refer to 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 nifedipine exposure to the infant are not known (see Section 4.6).

In patients with mild, moderate or severe impaired liver function, careful monitoring, and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.2 and 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 enzyme system. Concomitant use of substances that are known to inhibit or induce this enzyme system may lead to increased or reduced plasma concentrations of nifedipine. Changes in the dose of nifedipine may be required (see section 4.5).

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 (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.

Drugs decreasing nifedipine exposure:

• rifampicin (see above)

• phenytoin

• carbamazepine

- phenobarbital

Effects of nifedipine on other drugs

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

When nifedipine is administered simultaneously with 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 co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug food interactions

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice.

Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (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

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine (see Section 4.4).

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

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

From the clinical evidence available a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (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 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

Nifedipine may cause dizziness, lethargy and visual disturbances. Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or use machinery. This applies particularly at the start of treatment, when changing the medication, and in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below: ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

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

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
Metabolism and Nutrition Disorders			
			Hyperglycaemia
Immune System Disorders			
	Allergic reaction Allergic oedema/angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	Anaphylactic/anaphylactoid reaction
Psychiatric Disorders			
	Anxiety reactions Sleep disorders		
Nervous System Disorders			
Headache	Vertigo	Par-/Dysaesthesia	Hypoaesthesia, Somnolence

	Migraine Dizziness Tremor		
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 Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	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, Connective Tissue and Bone 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.

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, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Treatment
As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. 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) should be considered 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).

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

Symptomatic 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: 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. Its main action is to relax arterial smooth muscle both in the coronary and peripheral circulation.
In angina pectoris, nifedipine capsules relax peripheral arteries so reducing the load on the left ventricle. Additionally, nifedipine dilates submaximally both clear and pre-stenotic, stenotic and post-stenotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Nifedipine capsules reduce 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.

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) IN SD-45,
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.

6.6 Special precautions for disposal

No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0311

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/09/2019