SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nifedipine 5mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Nifedipine 5.0mg.

Excipient with known effect:
Each capsule contains 40.14mg of Glycerin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oval dark brown, soft gelatin capsule.The capsules are size 3

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nifedipine capsules are indicated for the prophylaxis of chronic stable angina pectoris and the treatment of hypertension

4.2 Posology and method of administration

Posology

Adults

The recommended starting dose of nifedipine is 5mg every 8 hours swallowed with water with subsequent titration of dosage according to response. The dose may be adjusted to 20mg every 8 hours.

Elderly

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 liver problems

Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored. Patients with renal impairment should not require adjustment of dosage.

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

Method of administration

The capsules should be swallowed whole with a little water.

4.3 Contraindications

- Hypersensitivity to Nifedipine any of the excipients listed in section 6.1.or other dihydropyridines because of the theoretical risk of cross reactivity.
- Nifedipine should not be administered to patients with severe aortic stenosis or cardiogenic shock.
- Nifedipine should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.
- Nifedipine should be avoided in patients with a history of acute porphyria.
- 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 (see section 4.5).

4.4 Special warnings and precautions for use

Nifedipine should be used with caution in patients with hypotension or poor cardiac reserve. In patients with impaired liver function, careful monitoring and, in severe cases, a dose reduction may be necessary. Nifedipine may impair glucose tolerance, necessitating adjustment of antidiabetic treatment in diabetic patients.

Nifedipine may enhance the effects of other antihypertensive agents such as beta-blockers (although this combination is well tolerated) resulting in postural hypotension. Nifedipine will not prevent the occurrence of rebound effects following the discontinuation of other antihypertensive agents.

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. In some patients, treatment with short-acting nifedipine induces an exaggerated fall in blood pressure with reflex tachycardia which can cause myocardial ischaemia or other cardiovascular complications. Nifedipine should be stopped in patients who experience ischaemic pain following its administration.

Nifedipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blocker preferably over 8 - 10 days.

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. Treatment with short-acting nifedipine can cause cardiovascular complications such as 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 the treatment.

The occurrence of myocardial infarction has been described in isolated cases, although it was not possible to distinguish this from the natural course of the underlying disease.

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

Deterioration of heart failure has occasionally been observed with nifedipine.

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

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (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.

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 are not known (see section 4.6).

For use in special population 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 the following weak to moderate inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered. In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

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).

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).

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.

Further studies

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

Cytochrome P450 3A4 system inducing anti-epileptic drugs, such as phenytoin, carbamazepine and phenobarbitone
Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

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

Effects of nifedipine on other drugs

Blood pressure lowering drugs

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

- diuretics,
- β-blockers,
- ACE-inhibitors,
- Angiotensin 1(AT1) receptor- antagonists,
- other calcium antagonists,
- α-adrenergic blocking agents,
- PDE5 inhibitors,
- α-methyldopa

When nifedipine is administered simultaneously with beta-receptor blockers, the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

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.
Some authors reported increased plasma concentrations of nifedipine upon co-administration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine.

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

Tacrolimus
Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Phenytoin
Concurrent administration of nifedipine with phenytoin will lead to increased plasma phenytoin concentration.

Digoxin
The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in the 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.

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 of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice.
Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine.

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

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.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity.

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

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding

Nifedipine passes into the breast milk. The nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant (see section 4.4).

Fertility

In single cases of *in vitro* fertilisation, calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

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

Common ≥ 1% to <10%	Uncommon ≥ 0.1% to <1%	Rare ≥ 0.01% to <0.1%	Frequency Not Known
Blood and Lymphatic System Disorders			
			Agranulocytosis ***Leucopenia***
Immune System Disorder			
	Allergic reaction Allergic oedema / angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	***Anaphylactic/ anaphylactoid reaction***
Metabolism and Nutrition Disorders			
			Hyperglycaemia
Psychiatric Disorders			
	Anxiety reactions Sleep disorders		***Depression***
Nervous System Disorders			
Headache	Migraine Vertigo Dizziness Tremor	Dysaesthesia, paraesthesia, lethargy	***Hypoaesthesia,*** ***Somnolence***
Eye disorders			
	Visual disturbances		***Eye pain***
Cardiac Disorders			
	Tachycardia Palpitations		***Chest pain (Angina pectoris)***
Vascular Disorders			

Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic and Mediastinal Disorders			
	Nasal congestion Nosebleed		***Dyspnoea*** ***Pulmonary oedema******
Gastrointestinal Disorders			
Constipation	Gastrointestinal and abdominal pain Dyspepsia Flatulence Dry mouth, nausea	Gingival hyperplasia	***Vomiting, Bezoar*** ***Dysphagia,*** ***Intestinal obstruction,*** ***Intestinal ulcer,*** ***Gastroesophageal sphincter insufficiency***
Hepatobiliary Disorders			
	Transient increase in liver enzymes		***Jaundice***
Skin and Subcutaneous Tissue Disorders			
	Erythema		***Toxic Epidermal Necrolysis*** ***Photosensitivity allergic reaction*** ***Palpable purpura***
Musculoskeletal and Connective Tissue Disorders			
	Muscle cramps Joint swelling		***Myalgia, Arthralgia***
Renal and Urinary Disorders			
	Dysuria, Polyuria	Increased frequency of micturition	
Reproductive System and Breast Disorders			
	Erectile dysfunction		
General Disorders and Administration Site Conditions			
Feeling unwell	Unspecific pain Chills		

* = may result in life-threatening outcome

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

Calcium channel blockers, such as nifedipine, may contribute to the regulation of mood which in turn may increase the risk of suicide and depressive effects of these drugs. This is possibly because of their lipophilic properties in which they easily penetrate the blood-brain barrier. They have access to and may interfere with neurones and receptors involved in the regulation of mood.

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

Gingival hyperplasia and, in older men, gynaecomastia have been reported but these are usually reversible on drug withdrawal. Hypersensitivity reactions such as skin rashes and abnormalities of liver function have occurred. These symptoms disappear upon discontinuation of nifedipine. In dialysis patients with malignant hypertension and hypovolaemia, a distinct fall in blood pressure can occur as a result of vasodilation.

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

The symptoms of nifedipine overdose are not necessarily related to the quantity ingested. The following symptoms are observed in cases of severe nifedipine intoxication: Disturbances of consciousness to the point of coma, hypoxia, a drop in blood pressure, tachycardiac / bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, cardiogenic shock with pulmonary oedema.

Treatment-

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. After oral ingestion thorough

gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.

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.

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

3. Consider further doses of activated charcoal (alternatively ipecacuanha) every 4 hours, if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulphate).

4. Asymptomatic patients should be observed for at least 4 hours after ingestion.
Haemodialysis serves no purpose as nifedipine is not dialysable but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Hypotension should be treated with plasma expanders and elevation of the feet. Treatment of hypotension as a result of cardiogenic shock and arterial vasodilatation with calcium gluconate can be continued, with ECG monitoring. 10 - 20ml of 10% calcium gluconate should be administered intravenously over 5 - 10 minutes and repeated if necessary. As a result, the serum calcium can reach the upper normal range to slightly elevated levels.
Additionally, beta agonists should be given, e.g. 0.2mg isoprenaline as a slow IV injection or infused at a rate of 5mcg/min.

If these measures are insufficient, a vasoconstricting sympathomimetic should be given (e.g. dopamine or noradrenaline). The dosage of these drugs is determined solely by the effect obtained.
Bradycardiac heart rhythm disturbances may be treated symptomatically with beta-sympathomimetics or the use of a temporary pace-maker in life-threatening bradycardiac disturbances of heart rhythm.

Care should be taken to avoid cardiac overload when administering additional fluids or volume.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C08

Nifedipine is a dihydropyridine calcium-channel blocking agent which affects depolarisation by inhibiting cellular influx of calcium (thus maintaining the plateau phase of the action potential). Nifedipine administration produces vasodilatation. Peripheral vasodilatation reduces left ventricular load. Coronary vasodilatation (of pre-stenotic, stenotic, and post-stenotic arteries) protects the heart against coronary spasm and improves myocardial perfusion (thus providing beneficial effects in angina pectoris). Nifedipine also reduces blood pressure in hypertensive individuals.

Unlike other calcium antagonists, nifedipine has little or no effect on the sino-atrial or artrioventricular nodes and therefore exhibits no anti-arrhythmic activity.

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

The absorption of nifedipine from the gastro-intestinal tract is rapid and almost complete. It is subject to an appreciable first pass effect resulting in oral bioavailability of 45 to 75%. Peak plasma concentrations occur within 30 minutes and 4 hours of an oral dose. The plasma half-life is in the range of 2 to 5 hours. Plasma protein binding is between 92 and 98%. Metabolism occurs extensively in the liver by oxidation. This necessitates dosage reduction in hepatic impairment due to reduced clearance and increased elimination half-life. 70 to 80% of a dose is excreted in the urine almost entirely as inactive metabolites.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene Glycol 400

Glycerin 98%
Menthol
Saccharin Sodium
Purified Water

Capsule Shell Constituents:
Gelatin
Glycerin 98%
Black Iron Oxide (E172)
Red Iron Oxide (E172)
Yellow Iron Oxide (E172)
Titanium Dioxide (E171)
Purified Water

6.2 Incompatibilities

No major incompatibilities have been reported.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Keep out of the reach of children.
Protect from heat, light and moisture.

6.5 Nature and contents of container

Blister packed (10 capsules per strip) in PVC film/aluminium foil. Blister strips then packed into printed cartons.

Blister strip dimensions:
39 x 92 x 7.4mm.

Pack sizes: 20, 28, 56, 84, 100, 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0223

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of renewal:15/04/2009

10 DATE OF REVISION OF THE TEXT

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