For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

CALCIGARD
(Nifedipine capsules)

COMPOSITION
CALCIGARD-5
Each soft gelatin capsule contains:
Nifedipine I.P……5mg
Color: Sunset Yellow FCF
Excipients…….q. s

CALCIGARD-10
Each soft gelatin capsule contains:
Nifedipine I.P……10mg
Color: Sunset Yellow FCF
Excipients…….q. s

DOSAGE FORM
Soft gelatin capsules

INDICATIONS
I. Vasospastic Angina
It is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. Nifedipine may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina
(Classical Effort-Associated Angina)
It is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents. In chronic stable angina (effort-associated angina), nifedipine has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete. Controlled studies in small numbers of patients suggest concomitant use of nifedipine and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs.

POSOLOGY AND METHOD OF ADMINISTRATION

The dosage of nifedipine needed to suppress angina and that can be tolerated by the patient must be established by titration. Excessive doses can result in hypotension.

Therapy should be initiated with the 10 mg capsule. The starting dose is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective dose range is 10–20 mg three times daily. Some patients, especially those with evidence of coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, doses of 20–30 mg three or four times daily may be effective. Doses above 120 mg daily are rarely necessary. More than 180 mg per day is not recommended. In most cases, nifedipine titration should proceed over a 7–14-day period so that the physician can assess the response to each dose level and monitor the blood pressure before proceeding to higher doses. If symptoms so warrant, titration may proceed more rapidly provided that the patient is assessed frequently. Based on the patient's physical activity level, attack frequency, and sublingual nitroglycerin consumption, the dose of nifedipine may be increased from 10 mg t.i.d. to 20 mg t.i.d. and then to 30 mg t.i.d. over a three-day period.

In hospitalized patients under close observation, the dose may be increased in 10 mg increments over four- to six-hour periods as required to control pain and arrhythmias due to ischemia. A single dose should rarely exceed 30 mg. Avoid co-administration of nifedipine with grapefruit juice. No "rebound effect" has been observed upon discontinuation of nifedipine. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

CONTRAINDICATIONS

Nifedipine capsules must not be administered to patients with known hypersensitivity to the active substance, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
Nifedipine capsules must not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within 4 weeks of an acute myocardial infarction. Nifedipine capsules should not be used for the treatment of acute attacks of angina. The safety of Nifedipine capsules in malignant hypertension has not been established. Nifedipine capsules should not be used for secondary prevention of myocardial infarction. Nifedipine capsules should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Nifedipine capsules are not beta-blockers and therefore give 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.
Nifedipine capsules 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 capsules will not prevent possible rebound effects after cessation of other antihypertensive therapy.
Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg).
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 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.
Nifedipine capsules should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine capsules should be reserved for women with severe hypertension who are unresponsive to standard therapy. Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy. Nifedipine capsules are 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.
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. Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.
Nifedipine capsules 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.
The use of Nifedipine capsules 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.
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.
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 capsules contain yellow orange S (E110) which may cause allergic reactions.

DRUG-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. 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.
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. 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*
• *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.

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
Nifedipine capsules should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine.
In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity.
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, 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 breast-feeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant.
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.

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.

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”.

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	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 Nausea Dyspepsia Flatulence	Gingival hyperplasia	Vomiting Gastroesophageal sphincter insufficiency

		Dry mouth		
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.

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

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. 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 sulfate).

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 vasodilatation can be treated with calcium (10-20 ml of a 10 % calcium gluconate solution administered 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.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives, ATC code: C08CA05
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 capsules 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 capsules dilate submaximally both clear and pre-stenotic coronary arteries, and 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 capsules cause a reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Nifedipine capsules have 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.

PHARMACOKINETIC PROPERTIES
Absorption
After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulation (Nifedipine capsules) 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.

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 recommended maximum dose for humans.

EXPIRY DATE

Do not use later than the date of expiry.

PACKAGING INFORMATION

Calcigard-5 and Calcigard-10 is available in blister pack of 10 Capsules.

STORAGE AND HANDLING INSTRUCTIONS

Keep in a cool dry place, protected from light.

MARKETED BY

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IN/CALCIGARD 5,10mg/NOV-16/02/PI