Summary of Product Characteristics.

1. NAME OF THE MEDICINAL PRODUCT

Nifedelong 30, prolonged release tablets
Nifedelong 60, prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged tablet contains 30 or 60 mg nifedipine, respectively.
For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged release tablets.

4. CLINICAL PARTICULAR

4.1 Therapeutic indications.

a. Chronic stable angina
b. hypertension.

4.2 Posology and method of administration.

Adults:
Dosage must be adjusted according to each patient's needs. Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily.
Nifedilong Prolonged Release tablets should be swallowed whole and should not be bitten or divided. In general, titration should proceed over at 7-14 day period so that the physician can fully assess the response to each dose level and monitor blood pressure before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided the patient is assessed frequently. Titration to doses above 120 mg are not recommended.

Switch over from Nifedipine capsules to Nifedilong
Angina patients controlled on Nifedipine capsules alone or in combination with other antianginal medications may be safely switched to *Nifedilong Prolonged Release tablets* at the nearest, equivalent total daily dose (e.g. 1 Nifedipine capsule of 10 mg t.i.d. up to q.i.d. may be changed to 30 mg once daily of *Nifedilong Prolonged Release tablet*). Subsequent titration to higher doses may be necessary and should be initiated as clinically warranted. Experience with doses greater than 90 mg in patients with angina is limited. Therefore, doses greater than 90 mg should be used with caution and only when clinically warranted.
No "rebound effect" has been observed upon discontinuation of *Nifedilong Prolonged Release tablets*. However, if discontinuation of nifedipine is necessary the dosage should be decreased gradually with close physician supervision.

Switch over from Nifedipine tablets to Nifedilong
Patients controlled on Nifedipine tablets may be safely switched to *Nifedilong Prolonged Release tablets* at the nearest equivalent total daily dose (e.g. 1 Nifedipine tablet of 10 mg t.i.d. or 20 mg b.i.d. may be changed to 30 mg once daily of *Nifedilong Prolonged Release tablet*).

Co-administration with other Anti-anginal drugs
Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See Special Warnings and special Precautions, Interactions with other medicinal products, for information on co-administration of nifedipine with beta blockers or long acting nitrates.
As a rule, *Nifedilong Prolonged Release tablets* should be swallowed whole with a little water independently of mealtimes. Under no circumstances should they be chewed or broken up.
The medication is formulated in such way that it releases the active substance in the intestine with a practically constant rate over a 16 to 18 hour time period.

Elderly:
A slight alteration of the pharmacokinetics of nifedipine may be seen in the elderly.
Lower maintenance doses of nifedipine may be required compared to younger patients.

Children:
There are no recommendations for use in children.

Duration of use
The attending doctor will determine the duration of use.

4.3 Contraindications.

- Nifedilong should not be used in cases of known hypersensitivity to nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
- Nifedilong should not be used in cases of cardiovascular shock, clinically significant aortic stenosis or unstable angina.
- Nifedipine should not be used during or within one month of myocardial infraction.
- Nifedipine should not be used for the treatment of acute attacks of angina.
- Nifedipine should not be used for secondary prevention of myocardial infraction.
- Nifedipine should not be used in patients with a Kock pouch (ileostomy after proctocolectomy).
- Nifedipine should not be used in patients with inflammatory bowel disease or crohn`s disease
- Nifedipine should not be used in patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
- The safety of Nifedilong in malignant hypertension has not been established.
- Nifedipine should not be used during pregnancy before week 20 or during lactation.
- Nifedipine should not be used in combination with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction. (see Drug Interactions).
- Owing to the duration of action of the formulation, Nifedilong should not be administered to patients with hepatic impairment.

4.4 Special warnings and special precautions for use.

- The hypotensive effect of nifedipine in most patients is modest and well tolerated; however, occasional patients have had excessive and poorly tolerated hypotension during initial titration or at a time of subsequent upward dosage adjustment mostly in patients on concomitant β-blockers.
- Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a β-blocking agent who have undergone coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a β-blocking, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In patients treated with nifedipine where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the condition of the patient permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.
- Rarely, some patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increases. The mechanism of this response has not been established.
- Patients recently withdrawn from β-blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines.
  Initiation of nifedipine treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of β-blocker withdrawal and nifedipine initiation. It is important to gradually withdraw β-blocker therapy if possible, rather than stopping them abruptly before commencing nifedipine.
- Patients usually receiving a β-blocker, have rarely developed heart failure after beginning nifedipine.
- Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.
- **Liver insufficiency:** In patients with impaired liver function, careful monitoring and, in severe cases, a dose reduction may be necessary.

- *Hypotension:* Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested.

- Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm HG) or those treated with hypotensive medicines. In cases of manifest heart failure, and in the case of severe aortic stenosis. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (see Special Warnings).
- In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.
- *Peripheral Oedema:* Mild to moderate peripheral oedema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about 1 in 10 patients treated with nifedipine (Dose dependent). This oedema occurs primarily in the lower extremities. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.
- During the treatment of stable angina pectoris with nifedipine, pain in the chest region (under certain circumstances angina pectoris-like symptoms) can occur up to about 30 mins. or up to about 1 h after administration.
- Patients undergoing therapy with this drug should have regular medical check-ups.
- As with any other non-deformable material, caution should be used when administering Nifedilong in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of Nifedilong.
- 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 fetus. .
- Diabetic patients taking nifedipine may require adjustment of their control.
- A false positive effect may be experienced when performing a barium contrast x-ray.
- Nifedipine is metabolized 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.

4.5 Interactions with other medicinal products and other forms of interaction

The blood pressure lowering effect of nifedipine may be potentiated with other antihypertensive drugs.

- ***Inhibitors of the cytochrome P450 3A4:***
  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.
    - Macrolide antibiotics (e.g. erythromycin)
    - Anti-HIV protease inhibitors (e.g. ritonavir)
    - Azole anti-mycotics (e.g. ketoconazole)
    - Fluoxetine
    - Nefazodone
    - Quinupristin/dalfopristin
    - Cispride
    - Valproic acid
    - Cimetidine/Ranitidine

- ***Inducers of the cytochrome P450 3A4:***
  Upon co-administration of known 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.
    - Carbamazepine
    - Phenobarbital
    - Rifampicin (See contraindication)
    - High Protein-Bound Drugs (phenytoin, quinidine):

- ***Nifedipine/β-Adrenergic Blocking Agents****:*

(See Special Warnings).

Experience in over 1,400 patients in a non-comparative clinical trial has shown that concomitant administration of nifedipine and β-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Caution should be taken in patients receiving nifedipine together with β-blockers, who have undergone coronary bypass surgery using high dose fentanyl for anesthesia (See Special Warnings).

- ***Nifedipine/Long Acting Nitrates****:*

Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies, to evaluate the antianginal effectiveness of this combination.

- ***Nifedipine/Digitalis****:*

Administration of nifedipine with digoxin increased digoxin levels in 9 out of 12 normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in 13 patients with coronary artery disease. In an uncontrolled study of over 200 patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing nifedipine to avoid possible over-digitalisation or underdigitalisation.

- ***Nifedipine/Coumarin Anticoagulants****:*

There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

- ***Nifedipine/Tacrolimus***:

Caution is advised when using nifedipine simultaneously with
tacrolimus, since the dose of 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.

- **Diagnostic Interference:**

Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.
Nifedipine, like other calcium channel blockers, decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine-treated patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

- ***Grapefruit Juice*:**

Co-administration of nifedipine with grapefruit juice results in up to a 2-fold increase in AUC and C_{max}, due to inhibition of CYP3A4 related first-pass metabolism. This effect of grapefruit juice may last for at least 3 days. Administration of nifedipine with grapefruit juice is to be avoided.

- ***Other forms of interaction:***

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

4.6 Pregnancy and lactation

Use in pregnancy: As stated above, nifedipine is contraindicated in pregnancy before week 20.
In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity.
There are no adequate 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 after week 20 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.

Use in breastfeeding:
As stated above, nifedipine is contraindicated during lactation.

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 men who are repeatedly unsuccessful in fathering a child by in-vitro fertilization and if no other explanation can be found, calcium antagonists like nifedipine should be considered a possible reason.

4.7 Effects on ability to drive and use machines

Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This applies particularly at the start of the treatment, on changing the medication, and in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:
ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).
The frequencies of ADRs reported with nifedipine-containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥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 Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic, and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnoea
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea	Gingival hyperplasia	Bezoar Dysphagia Intestinal

		Dyspepsia Flatulence Dry mouth		obstruction Intestinal ulcer Vomiting Gastroesophageal sphincter insufficiency
Hepatobiliary Disorders		Transient increase in liver enzymes		Jaundice
Skin and Subcutaneous Tissue Disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling		Arthralgia Myalgia
Renal and Urinary Disorders		Polyuria Dysuria		
Reproductive System and Breast Disorders		Erectile dysfunction		
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		

* = may result in life-threatening outcome
In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

4.9 Overdose
Experience with nifedipine overdosage is limited. Generally, overdosage with nifedipine leading to pronounced hypotension, calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. Clearance of nifedipine would be expected to be prolonged in patients with impaired liver function. Since nifedipine is highly protein-bound, dialysis is not likely to be of any benefit.

The benefit of gastric decontamination is uncertain.
1. Consider activated charcoal (50 g for adult, 1 g/kg for children) if the patient presents within 1 hour of ingestion of the potentially toxic amount.
Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release 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.

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

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac/bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.
Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympathomimetics, atropine or a temporary cardiac pacemaker and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.
Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 ml of a 10% calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If the effects are inadequate the treatment can be continued, with ECG monitoring, with additional β-sympathomimetics (e.g. Isoprenaline 0.2 mg slowly i.v., if necessary as a continuous infusion of 5 µg/min). If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained.
Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

5. PHARMACOLOGY PROPERTIES

5.1 Pharmacodinamic Properties

ATC code: CO8CA05
Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without altering serum calcium concentrations.

Mechanism of Action
(A) Angina
The precise mechanisms by which inhibition of calcium influx relieves angina has not been fully determined, but includes at least the following two mechanisms:

1. Relaxation and prevention of coronary artery spasm
Nifedipine dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonvine-induced.
This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of nifedipine in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2. Reduction of oxygen utilization
Nifedipine regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

(B) Hypertension
The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and the resulting reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.
Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

5.2 Pharmacokinetics and Metabolism

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate after a *Nifedilong Prolonged Release tablet* dose and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma

concentrations at this plateau are maintained with minimal fluctuations over the 24 hours dosing interval. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate release Nifedipine capsule at t.i.d. dosing than with once daily *Nifedilong Prolonged Release tablet*. At steady-state the bioavailability of the *Nifedilong Prolonged Release tablet* is 86% relative to nifedipine capsules. Administration of the *Nifedilong Prolonged Release tablet* in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability.
Markedly reduced GI retention time over prolonged periods (i.e. short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations. Pharmacokinetics of *Nifedilong tablets* are linear over the dose range of 20 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.
Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately two hours.
Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the faeces in metabolized form, most likely as a result of biliary excretion. Thus, the pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in haemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Haemodynamics
Like other slow-channel blockers nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg systolic), but sometimes larger. With *Nifedilong Prolonged Release tablets*, these decreases in blood pressure are not accompanied by any significant change in heart rate. Haemodynamic studies in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects
Although, like other members of its class, nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction or sinus node recovery time or to slow sinus rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Carbomer, silica colloidal anhydrous, hypromellose, lactose monohydrate, magnesium stearate, eudragit E, macrogol 4000, povidone, ferric oxide red, talc, titanium dioxide.

6.2 Incompatibilities
Not applicable.

6.3 Special precautions for storage.
Store below 25°C .Keep in the original package to protect from light and humidity.The tablets must therefore only be removed from the foil immediately before use.

7. MANUFACTURER
VALPHARMA S.P.A., REPUBLIC OF SAN MARINO

8.Marketing Authorization Holder
CTS Chemical Industries Ltd., Kiryat Malachi.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in 01.2013