Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nifelease 20 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nifedipine 20 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated prolonged release tablet
Round, slightly biconvex, pink coated tablets with smooth surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prophylaxis of angina pectoris.

In the management of primary/essential hypertension and secondary hypertension.

4.2 Posology and method of administration

4.2.1 Dosage

Adults / Elderly:

The recommended dose is one tablet (20mg) twice daily with subsequent titration of dosage according to response; if necessary the individual dose may be increased to 40mg twice daily. Patients with hepatic dysfunction should be monitored carefully. No dosage adjustment is normally required in patients with renal dysfunction.

Therapy may be indefinitely continued.

Children:

Not recommended.

4.2.2 Administration

For oral administration only.

4.3 Contraindications

Unstable angina pectoris.
Use in patients hypersensitive to the active ingredient.
Use in patients with cardiogenic shock.
Use in the case of severe aortic stenosis.

Acute myocardial infarction
Concomitant use with rifampicine (substance for treatment of tuberculosis).
Use in women capable of child-bearing or to nursing mothers.

4.4 Special warnings and precautions for use

Careful medical monitoring is required in:

- Severe hypotension with a systolic blood pressure under 90 mmHg.
- Congestive heart failure.

Caution should be exercised in patients with haemodialysis with malignant hypertension and hypovolemia as a significant hypotension due to vasodilation may develop.

Treatment with short acting nifedipine may induce an abrupt fall in blood pressure as well as tachycardia, which could lead to a detrimental outcome [*for hypertension indication*].

There is some concern about increased mortality and morbidity in the treatment of ischaemic heart disease, especially at higher dosages. Treatment with short-acting nifedipine may exacerbate angina pectoris.
There is no evidence that short-acting nifedipine confers benefit in secondary prevention of myocardial infarction [*for ischaemic heart disease indication]*.

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

Nifedipine should be used with caution in patients with poor cardiac reserve or severe hypotension. Deterioration of heart failure has occasionally been observed with nifedipine.

The introduction of nifedipine therapy may induce attacks of ischaemic pain in some patients with angina pectoris commonly with 30 minutes of taking nifedipine. Should this occur treatment should be stopped.

Patients should be advised that nifedipine may modify patients performance at skilled tasks (driving, operating machinery, etc.) to a varying degree depending upon dosage and individual susceptibility.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The blood pressure-lowering effect of nifedipine may be potentiated by other antihypertensive drugs and tricyclic antidepressants. The combined use of nifedipine and nitrates enhances the effects on blood pressure and heart rate.

Diltiazem reduces the degradation of nifedipine. Concomitant use necessitates careful patient monitoring. Dose reduction of nifedipine may be necessary.

Some calcium-antagonists may enhance the negative inotropic effect if antiarrhythmic drugs such as amiodarone.

Due to its enzyme reducing effect rifampicin accelerates degradation of nifedipine. Rifampicin must not be used concomitantly with nifedipine, as nifedipine plasma concentration will be decreased.

Elimination of vincristine is decreased by nifedipine, which may increase the risk of side effects of vincristine. Dose reduction of vincristine may be necessary.

Concomitant use of nifedipine and cephalosporins (e.g. cefixime) and nifedipine increases the cephalosporin plasma level.

The antihypertensive effect of nifedipine may be potentiated by other antihypertensive drugs and tricyclic

antidepressants.

Use of nifedipine may be combined with diuretics and beta-adrenoceptor blockers in antihypertensive therapy. However, introduction of such concurrent treatment should be conducted with care, as a major lowering of blood pressure may be produced. Nifedipine will not protect against the effects of withdrawal of beta-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives.

Any such withdrawal should be a gradual reduction of the dose of beta-blocker over 8 to 10 days.

In combined therapy with quinidine, the quinidine plasma level must be monitored, as nifedipine can cause a marked increase in quinidine plasma levels.

Nifedipine may cause an increase in the plasma levels of digoxin or theophylline; control of the latter is recommended.

Cimetidine, and to a lesser extent, ranitidine, may lead to an increase in the nifedipine plasma level. Diltiazem decreases the clearance of nifedipine and therefore increases plasma nifedipine levels. Both drugs should be used together with caution and a reduction of the nifedipine dose may be necessary.

As with other dihydropyridines, nifedipine should not be taken with grapefruit juice because bioavailability is increased.

4.6 Pregnancy and lactation

Nifedipine is contra-indicated in all three trimesters of pregnancy because animal studies have produced evidence if teratogenic effects (malformations). No experience with use in humans is available.

Small amounts of nifedipine are excreted in breast milk. As not data is available on possible side effects on the infant, nursing mothers should stop breast-feeding if they need to take nifedipine during lactation.

4.7 Effects on ability to drive and use machines

The occurrence of reactions, which may differ in severity from one person to another, may impair the patient's ability to drive vehicles and to operate machinery. This precaution applies particularly at the beginning of therapy, or when dosage is changed, or with concurrent consumption of alcohol.

4.8 Undesirable effects

Most side-effects are due to the hypotensive action of nifedipine. Especially at the beginning of treatment, headaches, flushing, and a sensation of warmth have been reported.

Occasionally, tachycardia, palpitations, lower leg oedema (due to vasodilatation), fatigue or vertigo may occur. Occasionally, paraesthesia and a blood pressure reduction below normal (hypotensive circulatory reaction) may also occur.

In rare cases, nausea, diarrhoea, allergic reactions and in individual cases photosensitivity and exfoliative dermatitis have been reported. Also micturition difficulties, impotence or tremors. Other less frequent reported side-effects include myalgia, tremor and visual disturbances.

There have been isolated reports of agranulocytosis, acute allergic reaction such as swelling of the skin and mucosa, angio-edema, bronchospasm and life threatening dyspnea reversible upon discontinuation.

In elderly patients especially on long-term therapy there have been rare reports of gynecomastia, resolved upon discontinuation of the drug in all cases so far.

In individual cases, an increase in the blood sugar level in the serum (hyperglycaemia) has been observed. This should be taken into account in patients suffering from diabetes mellitus.

In single cases syncopal episodes due to blood pressure reduction may occur during nifedipine treatment.

Especially at the start of therapy, patients may occasionally experience anginal attacks or patients with pre-existing angina pectoris may occasionally experience an increase in the frequency, duration and severity of anginal attacks. There have been isolated reports of myocardial infarction.

Patients with renal insufficiency may experience transient worsening of kidney function with nifedipine.

Caution must be exercised in dialysis patients with malignant hypertension and hypovolemia because they experience a significant blood pressure fall through vasodilation. Moreover, daily urinary output may be increased in the first weeks of therapy.

Very rarely, on long term treatment, gingival hyperplasia has been reported as well as a few cases of liver dysfunction (intrahepatic cholestasis, increases in transaminases) or hypersensitivity type jaundice.

These reactions normally regress on discontinuing therapy.

4.9 Overdose

Symptoms: Flushing, headache, increased heart rate, hypotension.

Reports of overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension, bradycardia and unconsciousness have been observed.

Gastric lavage and charcoal instillation have been employed.

Intravenous calcium gluconate or calcium chloride appear most helpful for treatment of hypotension, with intravenous atropine and/or beta-sympathomimetics for bradycardia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nifedipine is a vasodilator slow calcium channel antagonist. Its main action is to relax arterial smooth muscle in the coronary and peripheral circulation.

5.2 Pharmacokinetic properties

Nifedipine is well absorbed with an elimination half life of 2 to 5 hours. Systemic bioavailability is 50 - 70 % due to first-pass metabolism. Peak plasma concentrations are reached after 15 to 75 minutes for the immediate release formulations and 2 to 5 hours for the modified release preparation.

Its hypotensive effect extends to 6 to 8 hours maximum for the immediate release formulations and 10 to 12 hours maximum for the modified release preparation.

The drug is metabolised to inactive substances and excreted mostly via the kidney. The drug is strongly protein bound (approx. 95%).

5.3 Preclinical safety data

Acute toxicity and chronic toxicity studies have been carried out on various animal studies. No toxic effects were observed. No tumorigenic or mutagenic potential has been noted. However, teratogenic effects were observed in studies on three species of animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hypromellose type 2910
Lactose monohydrate
Macrogol 6000
Magnesium stearate
Maize starch
Polysorbate 80
Talc
Titanium dioxide E172
Red iron oxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Al/PVC blister packs in a cardboard outer container. Pack sizes 10, 20, 50, 100.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastraße 2-18
61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 04 April 2002

10 DATE OF REVISION OF THE TEXT

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