

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTES OF ADMINISTRATION, APPLICANTS, MARKETING
AUTHORISATION HOLDERS IN THE MEMBER STATES**

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Belgium		International Pharmaceutical Services (IPS), Jozef Nellenslei 10, 2100 Deurne, Belgium	Nifedipine TEVA 30/60 mg retard	30 mg / 60 mg	prolonged-release tablets	Oral use
Netherlands	Pharmamatch BV, Stationsweg Oost 281-D, 3931 ER Woudenberg, The Netherlands		Nifedipine Pharmamatch retard 30/60 mg	30 mg / 60 mg	prolonged-release tablets	Oral use
United Kingdom		Neolab Ltd., 57 High Street, Odiham, Hants, RG29 1LF United Kingdom	Neozipine XL 30/60 mg	30 mg / 60 mg	prolonged-release tablets	Oral use

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES
OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET
PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF NIFEDIPINE PHARMAMATCH RETARD 30/60 mg and associated names (See Annex I)

To date, limited data on exposed first trimester pregnancies have not shown an increase in the frequency of congenital anomalies compared to the frequency in the general population. In addition, in some cases, the use of nifedipine in order to treat pregnant hypertensive women is necessary. There are situations when other treatment alternatives are not suitable or where calcium antagonists are appropriate to include in a combination of different drugs after careful benefit/risk evaluation. Thus, contraindicating the use of nifedipine in women of childbearing potential, which amounts to contraindicating it from the beginning of the first trimester of pregnancy, should result in a loss of chance in this target population since nifedipine cannot be considered as a teratogenic product. It is a fact that there are nifedipine products on the EU market which are not contraindicated neither in pregnancy nor in women capable of child bearing. In conclusion, the warning related to women of childbearing potential proposed by the applicant in section 4.6 Pregnancy and lactation is relevant and sufficient.

There are limited data showing that nifedipine is excreted into human breast milk at low levels. It cannot be excluded that the newborn may be affected. However, the CHMP does not find it justified to contraindicate use in nursing mothers. Thus, the proposed wording in section 4.6. of the SmPC to avoid breastfeeding during treatment when necessary, is sufficient.

In conclusion, the benefit/risk ratio favours the opinion that the use of nifedipine should not be contraindicated for women capable of childbearing or for nursing women.

GROUND FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- The scope of the referral was to agree whether nifedipine should be contraindicated for women capable of childbearing or for nursing women and to amend the Summary of Products Characteristics in view of the available safety data
- The Summary of Products Characteristic, labelling and package leaflet proposed by the applicant has been assessed based on the documentation submitted, the scientific discussion within the Committee and the new wording proposed in the updated Guideline on SPC dated October 2005 and the latest QRD templates version 7

The CHMP has recommended the granting of the Marketing Authorisation(s) for which the Summaries of Product Characteristics, labelling and package leaflet are set out in Annex III for Nifedipinr Pharmamatch Retard 30/60 mg and associated names (see Annex I).

ANNEX III

**AMENDED SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND
PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 30 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 30 mg nifedipine.

Excipients:

Titanium dioxide (E172): colouring aid

Red iron oxide (E172): colouring aid

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

Round, biconvex tablets with a pale red colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris as monotherapy or in combination with a beta-blocker.

For the treatment of all grades of hypertension.

4.2 Posology and method of administration

For oral administration.

Treatment should be titrated for optimal effect according to individual needs of the patient.

Depending on the clinical symptoms, the standard dosage should be gradually increased.

The following posology is recommended for adults:

For chronic stable angina pectoris (exertion-induced angina):

The recommended initial dose is one 30mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90 mg once-daily.

For hypertension:

The recommended initial dose is one 30mg tablet once-daily. If necessary the dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

The tablets should be swallowed whole and should not be bitten, chewed or crushed. Preferably the tablets are administered in the morning with a glass of water (no grapefruit juice; see also section 4.5).

The treating physician decides on the duration of treatment.

Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30mg Nifedipine Pharmamatch retard once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically

Hepatic impairment:

In patients with hepatic impairment careful monitoring is required and, in severe cases, a lowering of the dose may be necessary.

Renal impairment:

Patients with renal impairment should not require adjustment of dosage.

Children and adolescents:

Nifedipine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to nifedipine or other dihydropyridines, or to any of the excipients.
- Pregnancy (See section 4.6).
- Cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris, or during or within one month of a myocardial infarction.
- The use of rifampicin.

4.4 Special warnings and special precautions for use

In exceptional cases, the use of nifedipine can lead to severe complaints of angina pectoris, probably due to fast resorption and an overly abrupt decrease in blood pressure. Whenever this is the case, the treating physician should be notified immediately, and treatment with nifedipine should be ceased.

Nifedipine can aggravate an existing *decompensatio cordis* in:

- patients with an obstruction of the out-flow tract, in which an increase of the gradient of the decompensation sometimes occurs (e.g. aorta stenosis) (See section 4.3);
- patients with a right-sided *decompensatio cordis*, in which in some cases a decrease of cardiac output, accompanied with increased fluid retention, occurs.

Nifedipine should be used with caution in patients with (threatening) ischemia of fingers and/or toes, because this can be worsened due to decreased tissue perfusion as a result of a lower perfusion pressure.

In patients with diarrhoea, the residence time of the tablet in the gastrointestinal tract, and as a result thereof, the duration of action are decreased.

Since symptoms of obstruction can occur in patients with pre-existing severe gastrointestinal narrowing, Nifedipine Pharmamatch retard should not be administered to those patients.

Symptoms of obstruction have also been seen in patients in which no gastrointestinal narrowing was diagnosed. Nifedipine Pharmamatch retard should neither be prescribed to patients with Kock pouch (ileostomy after proctocolectomy).

Special care is needed in case of very low blood pressure (severe hypotension with systolic pressure below 90 mmHg).

Caution should be exercised in patients with hypotension, as there is a risk of further reduction in blood pressure.

The possibility of an additive effect resulting in postural hypotension should be borne in mind when Nifedipine Pharmamatch retard is used in combination with other beta-blocking medicinal products and antihypertensive agents. Nifedipine Pharmamatch retard will not prevent possible rebound effects after cessation of other antihypertensive therapy.

It should not be used for secondary prevention of myocardial infarction.

It should not be used for acute attacks of angina.

Safety in malignant hypertension is not established.

Diabetic patients taking Nifedipine Pharmamatch retard may require adjustment of their control. In patients with possible hyperglycaemia, nifedipine should be given with caution.

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

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

In vitro fertilisation

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.

4.5 Interaction with other medicinal products and other forms of interaction

Nifedipine is metabolised via the cytochrome P450 3A4 system (CYP3A4), which is present in the intestinal mucosa and the liver. Medicines that are known to either inhibit or induce this enzyme can therefore alter the absorption (after oral administration) or elimination of nifedipine.

Substances that induce CYP3A4

Rifampicin

Rifampicin strongly induces the CYP3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is markedly reduced (95% decrease of AUC) and thus its efficacy weakened. Co-administration of nifedipine with rifampicin is therefore contra-indicated.

Phenytoin

Phenytoin induces the CYP3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced (70% decrease of AUC) and thus its efficacy weakened. When both medicines 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 medicines, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

Substances that inhibit CYP3A4

Grapefruit juice

Grapefruit juice inhibits the CYP3A4 system. Co-administration of grapefruit juice with nifedipine causes elevated plasma concentrations of nifedipine, due to a decreased first pass metabolism. 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. The intake of grapefruit juice during treatment with nifedipine is discouraged (see also section 5.2).

Cimetidine

Due to inhibition of the CYP3A4 system, cimetidine increases the plasma concentration of nifedipine, and therefore the antihypertensive effect of nifedipine may be potentiated. This should be considered during treatment of hypertension.

Erythromycin, fluoxetine, protease-inhibitors and azole-derivatives

No clinical interaction studies have been performed between nifedipine and active substances that inhibit the CYP3A4 system, like erythromycin, fluoxetine, protease-inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir) and azole-derivatives (ketoconazole, itraconazole and fluconazole). Some of these substances, like fluoxetine, indinavir and ritonavir, have been demonstrated to inhibit the CYP3A4 mediated metabolism of nifedipine *in vitro*. Co-administered of the mentioned medicines with nifedipine can be expected to lead to a substantial increase in bioavailability of nifedipine, due to a decreased first pass metabolism and decreased elimination. In case of concomitant use, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Other interactions with nifedipine

Carbamazepine, phenobarbitone and valproic acid

Some substances have been shown to influence the plasma concentration of the structurally related calcium antagonist nimodipine, either by enzyme induction (carbamazepine, phenobarbitone) or enzyme inhibition (valproic acid). Therefore, a decrease or an increase in nifedipine plasma concentrations and hence an alteration in efficacy cannot be excluded.

Antihypertensive medicines

The blood pressure lowering effect of nifedipine can be induced in case of co-administration with other antihypertensive medicines.

In case of co-administration of nifedipine with β -blocking medicines, the patient should be carefully monitored, since severe hypotension can occur. Furthermore, a deterioration of heart failure can occur.

Quinidine

Some studies reveal increased plasma concentrations of nifedipine in case of co-administration with quinidine, though others revealed no effects on the pharmacokinetic properties of nifedipine. If quinidine is added to an existing nifedipine therapy, blood pressure should be carefully monitored. If necessary, the nifedipine dosage should be reduced (see also subsection 'Effects of Nifedipine Pharmamatch retard on other active substances').

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (C_{max} increase of 33% compared to placebo). In case of concomitant use of both medicines, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Diltiazem

Diltiazem decreases the clearance of nifedipine. Caution should be taken when both medicines are used in combination. A reduction of the nifedipine dose can be considered.

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. In case of concomitant use of both medicines, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Digoxin

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. As a precaution, the patient should be examined for symptoms of digoxin overdose and, if necessary, a reduction of the glycoside-dosage should be considered, taking into account the plasma concentration of digoxin.

Quinidine

In individual cases, when used in combination with nifedipine, serum quinidine levels have been shown to be suppressed or, after cessation of nifedipine treatment, increased. Therefore, monitoring of quinidine plasma levels is recommended. If necessary, adjustment of the quinidine dosage is recommended when treatment with nifedipine is started or ceased during treatment with quinidine (see also subsection 'Interactions of other medicines with Nifedipine Pharmamatch retard').

Diuretics

When nifedipine is added to therapy with a diuretic, a temporary induced saluretic effect can occur, and a pre-existing hypokalaemia can be induced.

Intravenous magnesium sulphate

Caution should be exercised when nifedipine is co-administered with intravenous magnesium sulphate. In individual cases of concomitant use, neuromuscular block has been observed.

Tacrolimus

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Published data show that in individual cases the tacrolimus dose can be reduced when co-administered with nifedipine. Upon co-administration of both medicines, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Medicines that do not influence Nifedipine Pharmamatch retard or are not influenced by Nifedipine Pharmamatch retard.

Co-administration of nifedipine with 100 mg acetylsalicylic acid, benazepril, candesartancilexetil, doxazosin, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone or triamterene/hydrochlorothiazide does not affect the pharmacokinetics of nifedipine.

Co-administration of nifedipine with 100 mg acetylsalicylic acid does not alter the effect of acetylsalicylic acid on platelet aggregation or bleeding time.

When used concomitantly, nifedipine does not affect the pharmacokinetics of candesartancilexetil, cerivastatin or irbesartan.

Other types of interactions

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

4.6 Pregnancy and lactation

There are no adequate data from the use of nifedipine in pregnant women. Studies in animals have shown reproductive toxicity, consisting of embryotoxicity and teratogenic effects at maternally toxic doses. Nifedipine is contraindicated during pregnancy (See section 4.3). Nifedipine should not be used by women who intend to get pregnant in the near future (see section 4.4).

Use in breast-feeding mothers

Nifedipine is excreted into breast milk in small amounts. It is not known if a pharmacological effect in the infant can occur because of this; however, it is recommended to cease breast feeding as a precautionary measure.

4.7 Effects on ability to drive and use machines

In patients that experience dizziness, headache, fatigue or nausea, impaired reaction time may affect ability to drive or to operate machinery. This occurs especially at the beginning of treatment, in case of a change in medication or in case of concomitant use of alcohol.

4.8 Undesirable effects

Frequency of undesirable effects is classified as very common (>10%); common (1-10%); uncommon (0.1-1%); rare (0.01-0.1%) or very rare including isolated reports (<0.01%).

Adverse reactions are often dose related and occur most frequently in the first couple of weeks after initiation of therapy.

Cardiovascular disorders:

- *Very common:* peripheral oedema, flushing (facial reddening).

- *Common:* angina upon abrupt withdrawal of nifedipine, increased frequency or worsening of angina, aggravation of myocardial ischemia including myocardial infarction, palpitations (tachycardia – accelerated pulse rate), congestive heart failure, hypotension, orthostatic hypotension.
- *Uncommon:* ventricular arrhythmias, conduction disturbances, exacerbation of supraventricular arrhythmias, digital blood flow reduction in patients with Raynaud's syndrome.
- *Very rare:* pulmonary oedema, syncope, heart block.

Respiratory, thoracic and mediastinal disorders:

- *Very rare:* pulmonary oedema

Gastrointestinal disorders:

- *Common:* constipation, nausea.
- *Uncommon:* oesophageal reflux in patients with systemic sclerosis, allergic hepatitis, increased portal pressure in patients with alcoholic cirrhosis, transient increase in liver enzymes.
- *Rare:* bezoars, gingival hyperplasia after long-term treatment which recedes completely at discontinuation of nifedipine.

Nervous system disorders:

- *Uncommon:* paresthesia of the extremities (arms and legs), finger twitching.
- *Very rare:* depression.

Blood and lymphatic system disorders:

- *Very rare:* aplastic anaemia, increase in serum potassium when nifedipine is combined with propranolol.

Endocrine disorders:

- *Rare:* gynaecomastia in men over 50 years; reversible at discontinuation of treatment.

Skin and subcutaneous tissue disorders:

- *Rare:* skin rash.
- *Very rare:* exfoliative dermatitis, Steven-Johnsons syndrome, erythema multiforme, urticaria, fixed drug eruption, pemphigus, phototoxicity.

Musculoskeletal and connective tissue disorders:

- *Rare:* muscle cramps.

Reproductive system and breast disorders:

- *Uncommon:* atrophic endometrium.
- *Very rare:* nocturnal enuresis, acute, reversible deterioration in renal function in patients with chronic renal insufficiency.

Eye disorders:

- *Uncommon:* eye reactions such as eye pain, temporary vision disturbances.

Ear and labyrinth disorders:

- *Very rare:* periorbital oedema, tinnitus.

General disorders and administration site conditions:

- *Very common:* headache, giddiness, light headedness, feeling of pressure in the head.

- *Common:* dizziness, tiredness.

- *Uncommon:* fever in the first few days after initiating therapy.

4.9 Overdose

Clinical effects

- Severe hypotension due to vasodilatation, and tachycardia or bradycardia are the most likely manifestations of overdose.
- Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia.
- Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.
- Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia, headache, red spots on the face, and unconsciousness to the point of coma

Treatment

Elimination of the active substance and the restoration of stable cardiovascular conditions have priority. After oral ingestion, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.

Especially for prolonged-release products (Nifedipine Pharmamatch retard) elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Activated charcoal should be given in 4-hourly doses of 25g for adults, 10g for children if nifedipine has been digested accidentally.

Haemodialysis is not useful, since nifedipine cannot be dialysed. However, plasmaferesis can be recommended (high plasma protein-binding, relatively small volume of distribution).

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Bradycardia can be treated symptomatically with atropine or with β -sympathomimetics, like isoprenaline. In case of life-threatening bradycardia, a temporary cardiac pacemaker can be used.

Hypotension as a result of cardiogenic shock and arterial vasodilatation should be treated with calcium (10-20 ml of calcium gluconate 10% slowly i.v., to be repeated if necessary). As a result of this treatment, the serum calcium levels can reach or exceed the upper limit of normal levels. If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, β -sympathomimetics may be given, e.g. 0.2 mg isoprenaline slowly i.v. or as a continuous infusion of 5 mg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these medicines should be determined by the patient's response.

Additional fluids should be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08CA05

Pharmacotherapeutic group: Calcium antagonists.

Nifedipine is a calcium antagonist and has a spasmolytic effect on the vascular wall of mainly coronary arteries.

As a result of the relaxation of arterial muscle, nifedipine reduces peripheral resistance, leading to an improvement of peripheral blood flow whilst decreasing after-load. Therefore, Nifedipine Pharmamatch retard is effective in angina pectoris and hypertension.

In a clinical study, the effect of Nifedipine retard prolonged-release tablets on cardiovascular and cerebrovascular morbidity was studied. The primary end-point was the combination of stroke, MI (including sudden death), heart failure or death from any other cardiovascular cause (composite end-point).

This randomised, double blind, prospective study was carried out on an average population of patients with hypertension that, besides a blood pressure of 150/95 mm Hg or higher or a systolic blood pressure of >160 mm Hg, presented with at least one other cardiovascular risk factor. A total of 6321 patients (55-80 years) were treated during 3 to 4.8 years with Nifedipine Retard or a standard combination of diuretics (hydrochlorothiazide 25 mg + amiloride 5 mg). The results show that Nifedipine Retard demonstrates both a comparable antihypertensive effect and a comparable effect on the above-mentioned composite end-point.

Separate analysis of the individual end-points show little differences in incidence between the groups treated with nifedipine or diuretics of stroke (2.0% versus 2.3%), MI (2.9% versus 2.7%) and death caused by any other cardiovascular disease (0.4% versus 0.4%). The incidence of heart failure shows a difference between both treatments (0.9% versus 0.3%). Considering the design of the study, no conclusions can be drawn from the results of the separate analysis. Moreover, the number of reported symptomatic adverse events was higher in the group treated with nifedipine than in the control group. This could mainly be attributed to the increased incidence of peripheral oedema. The number of severe adverse events, as well as the number of reported metabolism-related adverse events such as hypokalaemia, hyponatraemia and hyperuremia, was lower in the group treated with nifedipine.

5.2 Pharmacokinetic properties

Absorption

Nifedipine is rapidly and almost completely absorbed (>90%). Bioavailability is approximately 40-60%.

Nifedipine Pharmamatch retard 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. Therefore, the tablets are appropriate for once-daily administration. An almost constant release rate provides a relatively constant concentration of active substance in plasma, without major differences between maximal and minimal levels.

It takes some time (lagtime of 2-4 hours) before the active substance escapes from Nifedipine Pharmamatch retard tablets. Moreover, as is the case for all oral administrations, the active substance undergoes a first pass effect.

Steady-state concentrations are already reached after administration of the second Nifedipine Pharmamatch retard tablet.

Co-administration of grapefruit juice reduces the first pass effect on nifedipine (see section 4.5). The pharmacokinetic properties of nifedipine in the Nifedipine Pharmamatch retard tablet are linear in a dose range of 30-180 mg. Based on the results of the bioequivalence studies, Nifedipine Pharmamatch retard tablets 30 mg and 60 mg can be considered to be bioequivalent to the reference product Adalat OROS under fasting and fed conditions.

Since it has been demonstrated that Nifedipine Pharmamatch retard tablets are bioequivalent with the nifedipine containing product Adalat OROS tablets, the Nifedipine Pharmamatch retard tablets are interchangeable with Adalat OROS tablets at all times.

Distribution

Both nifedipine and its metabolites are mainly bound to plasma protein (92-98%).

Metabolism

Nifedipine undergoes a first pass metabolism in the liver of 30-40%.

Nifedipine is almost entirely metabolised (> 90%); approximately 70-80% is excreted in urine. The two main metabolites are the pyridine-3-carbonic acid metabolite and a 2-hydroxymethyl-pyridine-3-carbonic acid metabolite or, depending on the pH, its lacton form. The metabolites are pharmacologically inactive and non-toxic.

Elimination

Nifedipine has a short half-life of approximately 2 – 4 hours. After release and absorption of the final dose the plasma concentration decreases, showing the same half-life values that were observed with oral formulations. In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. In severe cases, a lowering of the dose can be necessary.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In studies in mice, rats and rabbits, a dose which was maternally toxic induced teratogenic effects in some cases and embryotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E533b), titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Carton box with blister strips made of PVC/PVDC and aluminium foil.

Nifedipine Pharmamatch 30 mg tablets are available as prolonged-release tablets in a calendar packaging of 28 tablets (2 blisters of 14 tablets).

6.6 Instructions for use and handling <and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmamatch BV
Stationsweg Oost 281D
3930 EB Woudenberg
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

RVG 31822 – Nifedipine Pharmamatch retard 30 mg, prolonged-release tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29 November 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 60 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 60 mg nifedipine.

Excipients:

Titanium dioxide (E172): colouring aid

Red iron oxide (E172): colouring aid

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

Round, biconvex tablets with a pale red colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris as monotherapy or in combination with a beta-blocker.

For the treatment of all grades of hypertension.

4.2 Posology and method of administration

For oral administration.

Treatment should be titrated for optimal effect according to individual needs of the patient. Depending on the clinical symptoms, the standard dosage should be gradually increased.

The following posology is recommended for adults:

For chronic stable angina pectoris (exertion-induced angina):

The recommended initial dose is one 30mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90 mg once-daily.

For hypertension:

The recommended initial dose is one 30mg tablet once-daily. If necessary the dosage can be increased according to individual requirements up to a maximum of 90mg once-daily.

The tablets should be swallowed whole and should not be bitten, chewed or crushed. Preferably the tablets are administered in the morning with a glass of water (no grapefruit juice; see also section 4.5).

The treating physician decides on the duration of treatment.

Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30mg Nifedipine Pharmamatch retard once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically

Hepatic impairment:

In patients with hepatic impairment careful monitoring is required and, in severe cases, a lowering of the dose may be necessary.

Renal impairment:

Patients with renal impairment should not require adjustment of dosage.

Children and adolescents:

Nifedipine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to nifedipine or other dihydropyridines, or to any of the excipients.
- Pregnancy (See section 4.6).
- Cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris, or during or within one month of a myocardial infarction.
- The use of rifampicin.

4.4 Special warnings and special precautions for use

In exceptional cases, the use of nifedipine can lead to severe complaints of angina pectoris, probably due to fast resorption and an overly abrupt decrease in blood pressure. Whenever this is the case, the treating physician should be notified immediately, and treatment with nifedipine should be ceased.

Nifedipine can aggravate an existing *decompensatio cordis* in:

- patients with an obstruction of the out-flow tract, in which an increase of the gradient of the decompensation sometimes occurs (e.g. aorta stenosis) (See section 4.3);
- patients with a right-sided *decompensatio cordis*, in which in some cases a decrease of cardiac output, accompanied with increased fluid retention, occurs.

Nifedipine should be used with caution in patients with (threatening) ischemia of fingers and/or toes, because this can be worsened due to decreased tissue perfusion as a result of a lower perfusion pressure.

In patients with diarrhoea, the residence time of the tablet in the gastrointestinal tract, and as a result thereof, the duration of action are decreased.

Since symptoms of obstruction can occur in patients with pre-existing severe gastrointestinal narrowing, Nifedipine Pharmamatch retard should not be administered to those patients.

Symptoms of obstruction have also been seen in patients in which no gastrointestinal narrowing was diagnosed. Nifedipine Pharmamatch retard should neither be prescribed to patients with Kock pouch (ileostomy after proctocolectomy).

Special care is needed in case of very low blood pressure (severe hypotension with systolic pressure below 90 mmHg).

Caution should be exercised in patients with hypotension, as there is a risk of further reduction in blood pressure.

The possibility of an additive effect resulting in postural hypotension should be borne in mind when Nifedipine Pharmamatch retard is used in combination with other beta-blocking medicinal products and antihypertensive agents. Nifedipine Pharmamatch retard will not prevent possible rebound effects after cessation of other antihypertensive therapy.

It should not be used for secondary prevention of myocardial infarction.

It should not be used for acute attacks of angina.

Safety in malignant hypertension is not established.

Diabetic patients taking Nifedipine Pharmamatch retard may require adjustment of their control. In patients with possible hyperglycaemia, nifedipine should be given with caution.

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

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

In vitro fertilisation

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.

4.5 Interaction with other medicinal products and other forms of interaction

Nifedipine is metabolised via the cytochrome P450 3A4 system (CYP3A4), which is present in the intestinal mucosa and the liver. Medicines that are known to either inhibit or induce this enzyme can therefore alter the absorption (after oral administration) or elimination of nifedipine.

Substances that induce CYP3A4

Rifampicin

Rifampicin strongly induces the CYP3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is markedly reduced (95% decrease of AUC) and thus its efficacy weakened. Co-administration of nifedipine with rifampicin is therefore contra-indicated.

Phenytoin

Phenytoin induces the CYP3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced (70% decrease of AUC) and thus its efficacy weakened. When both medicines 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 medicines, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

Substances that inhibit CYP3A4

Grapefruit juice

Grapefruit juice inhibits the CYP3A4 system. Co-administration of grapefruit juice with nifedipine causes elevated plasma concentrations of nifedipine, due to a decreased first pass metabolism. 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. The intake of grapefruit juice during treatment with nifedipine is discouraged (see also section 5.2).

Cimetidine

Due to inhibition of the CYP3A4 system, cimetidine increases the plasma concentration of nifedipine, and therefore the antihypertensive effect of nifedipine may be potentiated. This should be considered during treatment of hypertension.

Erythromycin, fluoxetine, protease-inhibitors and azole-derivatives

No clinical interaction studies have been performed between nifedipine and active substances that inhibit the CYP3A4 system, like erythromycin, fluoxetine, protease-inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir) and azole-derivatives (ketoconazole, itraconazole and fluconazole). Some of these substances, like fluoxetine, indinavir and ritonavir, have been demonstrated to inhibit the CYP3A4 mediated metabolism of nifedipine *in vitro*. Co-administered of the mentioned medicines with nifedipine can be expected to lead to a substantial increase in bioavailability of nifedipine, due to a decreased first pass metabolism and decreased

elimination. In case of concomitant use, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Other interactions with nifedipine

Carbamazepine, phenobarbitone and valproic acid

Some substances have been shown to influence the plasma concentration of the structurally related calcium antagonist nimodipine, either by enzyme induction (carbamazepine, phenobarbitone) or enzyme inhibition (valproic acid). Therefore, a decrease or an increase in nifedipine plasma concentrations and hence an alteration in efficacy cannot be excluded.

Antihypertensive medicines

The blood pressure lowering effect of nifedipine can be induced in case of co-administration with other antihypertensive medicines.

In case of co-administration of nifedipine with β -blocking medicines, the patient should be carefully monitored, since severe hypotension can occur. Furthermore, a deterioration of heart failure can occur.

Quinidine

Some studies reveal increased plasma concentrations of nifedipine in case of co-administration with quinidine, though others revealed no effects on the pharmacokinetic properties of nifedipine. If quinidine is added to an existing nifedipine therapy, blood pressure should be carefully monitored. If necessary, the nifedipine dosage should be reduced (see also subsection 'Effects of Nifedipine Pharmamatch retard on other active substances').

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (C_{max} increase of 33% compared to placebo). In case of concomitant use of both medicines, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Diltiazem

Diltiazem decreases the clearance of nifedipine. Caution should be taken when both medicines are used in combination. A reduction of the nifedipine dose can be considered.

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. In case of concomitant use of both medicines, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Digoxin

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. As a precaution, the patient should be examined for symptoms of digoxin overdose and, if necessary, a reduction of the glycoside-dosage should be considered, taking into account the plasma concentration of digoxin.

Quinidine

In individual cases, when used in combination with nifedipine, serum quinidine levels have been shown to be suppressed or, after cessation of nifedipine treatment, increased. Therefore, monitoring of quinidine plasma levels is recommended. If necessary, adjustment of the quinidine dosage is recommended when treatment with nifedipine is started or ceased during treatment with quinidine (see also subsection 'Interactions of other medicines with Nifedipine Pharmamatch retard').

Diuretics

When nifedipine is added to therapy with a diuretic, a temporary induced saluretic effect can occur, and a pre-existing hypokalaemia can be induced.

Intravenous magnesium sulphate

Caution should be exercised when nifedipine is co-administered with intravenous magnesium sulphate. In individual cases of concomitant use, neuromuscular block has been observed.

Tacrolimus

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Published data show that in individual cases the tacrolimus dose can be reduced when co-administered with nifedipine. Upon co-administration of both medicines, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Medicines that do not influence Nifedipine Pharmamatch retard or are not influenced by Nifedipine Pharmamatch retard.

Co-administration of nifedipine with 100 mg acetylsalicylic acid, benazepril, candesartancilexetil, doxazosine, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone or triamterene/hydrochlorothiazide does not affect the pharmacokinetics of nifedipine.

Co-administration of nifedipine with 100 mg acetylsalicylic acid does not alter the effect of acetylsalicylic acid on platelet aggregation or bleeding time.

When used concomitantly, nifedipine does not affect the pharmacokinetics of candesartancilexetil, cerivastatin or irbesartan.

Other types of interactions

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

4.6 Pregnancy and lactation

There are no adequate data from the use of nifedipine in pregnant women. Studies in animals have shown reproductive toxicity, consisting of embryotoxicity and teratogenic effects at maternally toxic doses. Nifedipine is contraindicated during pregnancy (See section 4.3). Nifedipine should not be used by women who intend to get pregnant in the near future (see section 4.4).

Use in breast-feeding mothers

Nifedipine is excreted into breast milk in small amounts. It is not known if a pharmacological effect in the infant can occur because of this; however, it is recommended to cease breast feeding as a precautionary measure.

4.7 Effects on ability to drive and use machines

In patients that experience dizziness, headache, fatigue or nausea, impaired reaction time may affect ability to drive or to operate machinery. This occurs especially at the beginning of treatment, in case of a change in medication or in case of concomitant use of alcohol.

4.8 Undesirable effects

Frequency of undesirable effects is classified as very common (>10%); common (1-10%); uncommon (0.1-1%); rare (0.01-0.1%) or very rare including isolated reports (<0.01%).

Adverse reactions are often dose related and occur most frequently in the first couple of weeks after initiation of therapy.

Cardiovascular disorders:

- *Very common*: peripheral oedema, flushing (facial reddening).
- *Common*: angina upon abrupt withdrawal of nifedipine, increased frequency or worsening of angina, aggravation of myocardial ischemia including myocardial infarction, palpitations (tachycardia – accelerated pulse rate), congestive heart failure, hypotension, orthostatic hypotension.
- *Uncommon*: ventricular arrhythmias, conduction disturbances, exacerbation of supraventricular arrhythmias, digital blood flow reduction in patients with Raynaud's syndrome.
- *Very rare*: pulmonary oedema, syncope, heart block.

Respiratory, thoracic and mediastinal disorders:

- *Very rare*: pulmonary oedema

Gastrointestinal disorders:

- *Common*: constipation, nausea.
- *Uncommon*: oesophageal reflux in patients with systemic sclerosis, allergic hepatitis, increased portal pressure in patients with alcoholic cirrhosis, transient increase in liver enzymes.
- *Rare*: bezoars, gingival hyperplasia after long-term treatment, which recedes completely at discontinuation of nifedipine.

Nervous system disorders:

- *Uncommon*: paresthesia of the extremities (arms and legs), finger twitching.
- *Very rare*: depression.

Blood and lymphatic system disorders:

- *Very rare*: aplastic anaemia, increase in serum potassium when nifedipine is combined with propranolol.

Endocrine disorders:

- *Rare*: gynaecomastia in men over 50 years; reversible at discontinuation of treatment.

Skin and subcutaneous tissue disorders:

- *Rare*: skin rash.
- *Very rare*: exfoliative dermatitis, Steven-Johnsons syndrome, erythema multiforme, urticaria, fixed drug eruption, pemphigus, phototoxicity.

Musculoskeletal and connective tissue disorders:

- *Rare*: muscle cramps.

Reproductive system and breast disorders:

- *Uncommon*: atrophic endometrium.
- *Very rare*: nocturnal enuresis, acute, reversible deterioration in renal function in patients with chronic renal insufficiency.

Eye disorders:

- *Uncommon*: eye reactions such as eye pain, temporary vision disturbances.

Ear and labyrinth disorders:

- *Very rare*: periorbital oedema, tinnitus.

General disorders and administration site conditions:

- *Very common*: headache, giddiness, light headedness, feeling of pressure in the head.

- *Common*: dizziness, tiredness.

- *Uncommon*: fever in the first few days after initiating therapy.

4.9 Overdose

Clinical effects

- Severe hypotension due to vasodilatation, and tachycardia or bradycardia are the most likely manifestations of overdose.
- Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia.
- Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.
- Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia, headache, red spots on the face, and unconsciousness to the point of coma

Treatment

Elimination of the active substance and the restoration of stable cardiovascular conditions have priority. After oral ingestion, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.

Especially for prolonged-release products (Nifedipine Pharmamatch retard) elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Activated charcoal should be given in 4-hourly doses of 25g for adults, 10g for children if nifedipine has been digested accidentally.

Haemodialysis is not useful, since nifedipine cannot be dialysed. However, plasmaferesis can be recommended (high plasma protein-binding, relatively small volume of distribution).

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Bradycardia can be treated symptomatically with atropine or with β -sympathomimetics, like isoprenaline. In case of life-threatening bradycardia, a temporary cardiac pacemaker can be used.

Hypotension as a result of cardiogenic shock and arterial vasodilatation should be treated with calcium (10-20 ml of calcium gluconate 10% slowly i.v., to be repeated if necessary). As a result of this treatment, the serum calcium levels can reach or exceed the upper limit of normal levels. If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, β -sympathomimetics may be given, e.g. 0.2 mg isoprenaline slowly i.v. or as a continuous infusion of 5 mg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these medicines should be determined by the patient's response.

Additional fluids should be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08CA05

Pharmacotherapeutic group: Calcium antagonists.

Nifedipine is a calcium antagonist and has a spasmolytic effect on the vascular wall of mainly coronary arteries.

As a result of the relaxation of arterial muscle, nifedipine reduces peripheral resistance, leading to an improvement of peripheral blood flow whilst decreasing after-load. Therefore, Nifedipine Pharmamatch retard is effective in angina pectoris and hypertension.

In a clinical study, the effect of Nifedipine retard prolonged-release tablets on cardiovascular and cerebrovascular morbidity was studied. The primary end-point was the combination of stroke, MI (including sudden death), heart failure or death from any other cardiovascular cause (composite end-point).

This randomised, double blind, prospective study was carried out on an average population of patients with hypertension that, besides a blood pressure of 150/95 mm Hg or higher or a systolic blood pressure of >160 mm Hg, presented with at least one other cardiovascular risk factor. A total of 6321 patients (55-80 years) were treated during 3 to 4.8 years with Nifedipine Retard or a standard combination of diuretics (hydrochlorothiazide 25 mg + amiloride 5 mg). The results show that Nifedipine Retard demonstrates both a comparable antihypertensive effect and a comparable effect on the above-mentioned composite end-point.

Separate analysis of the individual end-points show little differences in incidence between the groups treated with nifedipine or diuretics of stroke (2.0% versus 2.3%), MI (2.9% versus 2.7%) and death caused by any other cardiovascular disease (0.4% versus 0.4%). The incidence of heart failure shows a difference between both treatments (0.9% versus 0.3%). Considering the design of the study, no conclusions can be drawn from the results of the separate analysis. Moreover, the number of reported symptomatic adverse events was higher in the group treated with nifedipine than in the control group. This could mainly be attributed to the increased incidence of peripheral oedema. The number of severe adverse events, as well as the number of reported metabolism-related adverse events such as hypokalaemia, hyponatraemia and hyperuremia, was lower in the group treated with nifedipine.

5.2 Pharmacokinetic properties

Absorption

Nifedipine is rapidly and almost completely absorbed (>90%). Bioavailability is approximately 40-60%.

Nifedipine Pharmamatch retard 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. Therefore, the tablets are appropriate for once-daily administration. An almost constant release rate provides a relatively constant concentration of active substance in plasma, without major differences between maximal and minimal levels.

It takes some time (lagtime of 2-4 hours) before the active substance escapes from Nifedipine Pharmamatch retard tablets. Moreover, as is the case for all oral administrations, the active substance undergoes a first pass effect.

Steady-state concentrations are already reached after administration of the second Nifedipine Pharmamatch retard tablet.

Co-administration of grapefruit juice reduces the first pass effect on nifedipine (see section 4.5). The pharmacokinetic properties of nifedipine in the Nifedipine Pharmamatch retard tablet are linear in a dose range of 30-180 mg. Based on the results of the bioequivalence studies, Nifedipine Pharmamatch retard tablets 30 mg and 60 mg can be considered to be bioequivalent to the reference product Adalat OROS under fasting and fed conditions.

Since it has been demonstrated that Nifedipine Pharmamatch retard tablets are bioequivalent with the nifedipine containing product Adalat OROS tablets, the Nifedipine Pharmamatch retard tablets are interchangeable with Adalat OROS tablets at all times.

Distribution

Both nifedipine and its metabolites are mainly bound to plasma protein (92-98%).

Metabolism

Nifedipine undergoes a first pass metabolism in the liver of 30-40%.

Nifedipine is almost entirely metabolised (> 90%); approximately 70-80% is excreted in urine. The two main metabolites are the pyridine-3-carbonic acid metabolite and a 2-hydroxymethylpyridine-3-carbonic acid metabolite or, depending on the pH, its lacton form. The metabolites are pharmacologically inactive and non-toxic.

Elimination

Nifedipine has a short half-life of approximately 2 – 4 hours. After release and absorption of the final dose the plasma concentration decreases, showing the same half-life values that were observed with oral formulations. In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. In severe cases, a lowering of the dose can be necessary.

5.3 Preclinical safety data

Preclinical data reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In studies in mice, rats and rabbits, a dose, which was maternally toxic induced teratogenic effects in some cases and embryotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E533b), titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Carton box with blister strips made of PVC/PVDC and aluminium foil.

Nifedipine Pharmamatch 60 mg tablets are available as prolonged-release tablets in a calendar packaging of 28 tablets (2 blisters of 14 tablets).

6.6 Instructions for use and handling <and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmamatch BV
Stationsweg Oost 281D
3930 EB Woudenberg

The Netherlands

- 8. MARKETING AUTHORISATION NUMBER(S)**
RVG 31823 – Nifedipine Pharmamatch retard 60 mg, prolonged-release tablets
- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
29 November 2004
- 10. DATE OF REVISION OF THE TEXT**

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 30 mg prolonged-release tablets
Nifedipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: 30 mg nifedipine

3. LIST OF EXCIPIENTS

Carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E553b) and titanium dioxide (E171).

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains lactose.

8. EXPIRY DATE

Do not use after:

9. SPECIAL STORAGE CONDITIONS

Store in the original packaging.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmamatch BV
Stationsweg Oost 281D
3930 EB Woudenberg
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch no.:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 30 mg prolonged-release tablets
Nifedipine.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

PM

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 60 mg prolonged-release tablets
Nifedipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: 60 mg nifedipine

3. LIST OF EXCIPIENTS

Carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E553b) and titanium dioxide (E171).

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains lactose.

8. EXPIRY DATE

Do not use after:

9. SPECIAL STORAGE CONDITIONS

Store in the original packaging.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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1. NAME OF THE MEDICINAL PRODUCT

Nifedipine Pharmamatch retard 60 mg prolonged-release tablets
Nifedipine.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

PM

3. EXPIRY DATE

Exp:

4. BATCH NUMBER

Batch:

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nifedipine Pharmamatch retard 30 mg prolonged-release tablets

Nifedipine

Read all of this leaflet carefully before you start taking using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Nifedipine Pharmamatch retard is and what it is used for
2. Before you take Nifedipine Pharmamatch retard
3. How to take Nifedipine Pharmamatch retard
4. Possible side effects
5. How to store Nifedipine Pharmamatch retard
6. Further information

1. WHAT NIFEDIPINE PHARMAMATCH RETARD IS AND WHAT IT IS USED FOR

Nifedipine Pharmamatch tablets are supplied in blister packs of 28.

Nifedipine is part of a group of medicines that relax and expand blood vessels (calcium antagonists). By doing so, the blood flow in the heart and limbs is improved, lowering blood pressure and preventing chest pain (angina pectoris).

- Nifedipine Pharmamatch retard is used to reduce the frequency of occurrence of a tight, painful chest ache caused by a shortage of oxygen in the heart muscle (angina pectoris). Nifedipine Pharmamatch retard may be used alone, or in combination with a medicine from another group of medicines called β -blockers.
- Nifedipine Pharmamatch retard is used to treat high blood pressure (hypertension).

2. BEFORE YOU TAKE NIFEDIPINE PHARMAMATCH

Do not take Nifedipine Pharmamatch retard

- if you are allergic (hypersensitive) to nifedipine or any of the other ingredients of Nifedipine Pharmamatch retard.
- if you are pregnant.
-
- if you have experienced a collapse which was caused by a heart problem (cardiogenic shock)
- if you have a narrowed aorta (aortic stenosis).
- if you suffer from unstable angina pectoris.
- if you had a heart attack less than a month ago.
- if you use the medicine rifampicin (a medicine used in certain infection disease).

Take special care with Nifedipine Pharmamatch retard

- if you suffer from decreased blood flow to the fingers and/or toes, caused by a narrowing of the veins (ischemia). Nifedipine can worsen the decreased blood flow.
- if you experience severe chest pains, or if the chest pains worsen. In such an event, you should stop taking Nifedipine Pharmamatch retard and contact your doctor.
- if the pumping force of the heart is insufficient (decompensatio cordis). Nifedipine can worsen an existing decompensatio cordis.

- if you suffer from diarrhoea. The duration of action of nifedipine can be shortened.
- if you have a severe narrowing of the gastrointestinal tract. Constipation (obstruction) can occur. Nifedipine Pharmamatch retard tablets must not be prescribed for these patients.
- if you use a stoma. You may not use this medicine in such a case.
- in case of *in vitro* fertilisation (IVF). Nifedipine can lower the chance of conception.
- if you have a low blood pressure (hypotension). Nifedipine can further lower the blood pressure.
- if you have diabetes. Diabetic patients who use Nifedipine Pharmamatch retard may require adjustment of their control.
- if you use other medicines for high blood pressure, since these medicines may increase the effect of Nifedipine Pharmamatch retard on blood pressure.
- if your blood pressure is continuing to rise despite treatment (malignant hypertension).

You should not use Nifedipine Pharmamatch retard to treat an angina attack when it occurs, but rather to reduce the frequency of the angina you experience over time.

You should not use Nifedipine Pharmamatch retard for secondary prevention of a heart attack.

Dosage in case of reduced liver function

If your liver function is lower than normal, your doctor can prescribe a lower dosage.

Dosage in case of reduced kidney function

Patients with renal impairment should not require adjustment of dosage.

Patients who are receiving kidney dialysis and have a very high blood pressure and low blood volume might experience a sudden drop in their blood pressure when they take Nifedipine Pharmamatch retard. If you are on kidney dialysis please consult your doctor before taking this medicine.

Use in children

Nifedipine is not recommended for use in children

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, notably rifampicin, including medicines obtained without a prescription.

Taking Nifedipine Pharmamatch retard with food and drink

The blood pressure lowering effect of nifedipine can be enhanced due to the intake of grapefruit juice. It is not recommended to drink grapefruit juice when treated with Nifedipine Pharmamatch retard.

It is recommended to take the Nifedipine Pharmamatch tablets in the morning with a glass of water (not grapefruit juice).

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

The safety of nifedipine during pregnancy has not been established. Nifedipine is contraindicated during pregnancy and not recommended in women who intend to get pregnant in the near future.

Breast-feeding

A small fraction of nifedipine passes into the breast milk. It is not known if this can lead to an effect in the infant. As a precaution, it is recommended to stop breast-feeding.

Driving and using machines

Nifedipine can cause dizziness, headache, fatigue or nausea, especially at the beginning of therapy, after a change in your medication or when consumed with alcohol. Therefore, the ability to drive or use machines can be reduced.

Important information about some of the ingredients of Nifedipine Pharmamatch retard

Nifedipine Pharmamatch retard contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE NIFEDIPINE PHARMAMATCH RETARD

Dosage

Always take Nifedipine Pharmamatch retard exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual initial dose is one 30mg tablet once-daily. If necessary, your doctor can increase the dosage to 90 mg once-daily.

How to take

You should not chew or break the tablets. It is recommended to take the tablets in the morning with a glass of water (not grapefruit juice).

Duration of treatment

Your doctor will determine the duration of treatment. Do not stop the treatment early without consulting your doctor.

If you take more Nifedipine Pharmamatch retard than you should

If you take more Nifedipine Pharmamatch retard than you should, immediately contact your doctor or pharmacist. Elimination of the product and the restoration of stable cardiovascular conditions may be needed.

If you take too much nifedipine a low blood pressure (hypertension) can occur, which can be recognised from symptoms like dizziness, nausea, vomiting, drowsiness, confusion, lethargy, flushing, a lack of oxygen (hypoxia), headache or red spots on the face. Eventually, unconsciousness can occur. Increased or decreased heart rates are also a symptom of overdose.

In the event of overdose it is recommended to lay down the patient with elevated legs, for instance by using some pillows.

If you forget to take Nifedipine Pharmamatch retard

If you have forgotten to take Nifedipine Pharmamatch retard, then do so as soon as possible. However, if it is already almost time to take the next dose (i.e. you skipped one day), skip the missed dose and continue to take the medicine according to the normal dosage scheme. In case of doubt, always contact your doctor or pharmacist.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Nifedipine Pharmamatch retard

If you suddenly stop using this medicine, the symptoms that you had before you started taking this medicine can come back. In case of doubt, always contact your doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nifedipine Pharmamatch retard can cause side effects, although not everybody gets them.

The following side effects can occur:

Very common (more than 1 out of 10 patients):

- headache
- flushing
- swelling, particularly of the ankles and legs

- giddiness
- light headedness
- feeling of pressure in the head.

Common (more than 1 out of 100, but less than 1 out of 10 patients):

- angina (upon sudden withdrawal of nifedipine)
- irregular heart beat (palpitations)
- heart failure
- tiredness
- constipation
- dizziness
- nausea
- increased frequency or worsening of angina
- increased shortage of oxygen in the heart, including a heart attack
- low blood pressure (hypotension)
- sudden low blood pressure that occurs when assuming a standing position (orthostatic hypotension).

Uncommon (more than 1 out of 1.000, but less than 1 out of 100 patients):

- heart rhythm disturbances
- increased sensitivity, particularly in arms and legs
- eye reactions such as eye pain, temporary vision disturbances
- finger twitching
- fever in the first few days after start of therapy
- transient increase in liver enzymes
- oesophageal reflux
- allergic liver infection
- increased blood pressure in the portal vein in patients with alcoholic cirrhosis
- degradation of the mucous membrane of the uterus (atrophic endometrium)
- reduction in blood flow to the fingers and toes (digital blood flow reduction) in patients with Raynaud's syndrome

Rare (more than 1 out of 10.000, but less than 1 out of 1.000 patients):

- skin rash
- muscle cramps
- inflammation of the gums
- a mass of foreign material found in the stomach (bezoar)
- a slight development in breast tissue in older men (gynaecomastia)

Very rare (Less than 1 out of 10.000 patients):

- bedwetting
- depression
- blistering of the skin when exposed to sunlight (phototoxicity)
- sudden worsening of kidney function in patients with chronic kidney problems
- swelling around the eyes (periorbital oedema)
- noise in the ear (tinnitus).
- moisture in lungs (pulmonary oedema)
- fainting (syncope)
- heart block
- peeling or flaking of skin (exfoliative dermatitis)
- severe blistering of the skin and/or mucous membranes of the lips, eyes, mouth, nasal passages or genitals (signs of Steven-Johnson syndrome)
- skin rashes (erythema multiforme, pemphigus, fixed drug eruption, urticaria)
- reduced production of red blood cells (aplastic anaemia)
- increase in blood potassium levels (when used together with another medicine called propranolol)
-

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NIFEDIPINE PHARMAMATCH RETARD

Keep out of the reach and sight of children.

Do not use Nifedipine Pharmamatch retard after the expiry date which is stated on the label carton after “Expiry date” or “exp.”. The first two numbers denote the month, the last two numbers denote the year. The expiry date refers to the last day of that month.

Store Nifedipine Pharmamatch retard tablets in the original packaging.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nifedipine Pharmamatch retard contains

- The active substance is nifedipine. Nifedipine Pharmamatch retard 30 mg, prolonged-release tablets contain 30 mg nifedipine per tablet.
- The other ingredients are: carbomer, colloidal silicon dioxide (E551), hypromellose (E464), lactose monohydrate, magnesium stearate (E572), methacrylic acid copolymer, macrogol, povidone (E1201), red iron oxide (E172), talc (E533b) and titanium dioxide (E171).

What Nifedipine Pharmamatch retard looks like and contents of the pack

Nifedipine Pharmamatch retard are prolonged-release tablets, which appear as round, biconvex tablets with a pale red colour.

Nifedipine Pharmamach retard tablets come in a calendar packing of 28 tablets (2 blisters of 14 tablets each).

Marketing Authorisation Holder and Manufacturer

Pharmamatch B.V.
Postbus 82
3930 EB Woudenberg
The Netherlands

This leaflet was last approved in {MM/YYYY}.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nifedipine Pharmamatch retard 60 mg prolonged-release tablets

Nifedipine

Read all of this leaflet carefully before you start taking using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Nifedipine Pharmamatch retard is and what it is used for
2. Before you take Nifedipine Pharmamatch retard
3. How to take Nifedipine Pharmamatch retard
4. Possible side effects
6. How to store Nifedipine Pharmamatch retard
6. Further information

2. WHAT NIFEDIPINE PHARMAMATCH RETARD IS AND WHAT IT IS USED FOR

Nifedipine Pharmamatch tablets are supplied in blister packs of 28.

Nifedipine is part of a group of medicines that relax and expand blood vessels (calcium antagonists). By doing so, the blood flow in the heart and limbs is improved, lowering blood pressure and preventing chest pain (angina pectoris).

- Nifedipine Pharmamatch retard is used to reduce the frequency of occurrence of a tight, painful chest ache caused by a shortage of oxygen in the heart muscle (angina pectoris). Nifedipine Pharmamatch retard may be used alone, or in combination with a medicine from another group of medicines called β -blockers.
- Nifedipine Pharmamatch retard is used to treat high blood pressure (hypertension).

4. BEFORE YOU TAKE NIFEDIPINE PHARMAMATCH

Do not take Nifedipine Pharmamatch retard

- if you are allergic (hypersensitive) to nifedipine or any of the other ingredients of Nifedipine Pharmamatch retard.
- if you are pregnant.
- if you have experienced a collapse which was caused by a heart problem (cardiogenic shock)
- if you have a narrowed aorta (aortic stenosis).
- if you suffer from unstable angina pectoris.
- if you had a heart attack less than a month ago.
- if you use the medicine rifampicin (a medicine used in certain infection disease).

Take special care with Nifedipine Pharmamatch retard

- if you suffer from decreased blood flow to the fingers and/or toes, caused by a narrowing of the veins (ischemia). Nifedipine can worsen the decreased blood flow.
- if you experience severe chest pains, or if the chest pains worsen. In such an event, you should stop taking Nifedipine Pharmamatch retard and contact your doctor.
- if the pumping force of the heart is insufficient (decompensatio cordis). Nifedipine can worsen an existing decompensatio cordis.

- if you suffer from diarrhoea. The duration of action of nifedipine can be shortened.
- if you have a severe narrowing of the gastrointestinal tract. Constipation (obstruction) can occur. Nifedipine Pharmamatch retard tablets must not be prescribed for these patients.
- if you use a stoma. You may not use this medicine in such a case.
- in case of *in vitro* fertilisation (IVF). Nifedipine can lower the chance of conception.
- if you have a low blood pressure (hypotension). Nifedipine can further lower the blood pressure.
- if you have diabetes. Diabetic patients who use Nifedipine Pharmamatch retard may require adjustment of their control.
- if you use other medicines for high blood pressure, since these medicines may increase the effect of Nifedipine Pharmamatch retard on blood pressure.
- if your blood pressure is continuing to rise despite treatment (malignant hypertension).

You should not use Nifedipine Pharmamatch retard to treat an angina attack when it occurs, but rather to reduce the frequency of the angina you experience over time.

You should not use Nifedipine Pharmamatch retard for secondary prevention of a heart attack.

Dosage in case of reduced liver function

If your liver function is lower than normal, your doctor can prescribe a lower dosage.

Dosage in case of reduced kidney function

Patients with renal impairment should not require adjustment of dosage.

Patients who are receiving kidney dialysis and have a very high blood pressure and low blood volume might experience a sudden drop in their blood pressure when they take Nifedipine Pharmamatch retard. If you are on kidney dialysis please consult your doctor before taking this medicine.

Use in children

Nifedipine is not recommended for use in children

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, notably rifampicin, including medicines obtained without a prescription.

Taking Nifedipine Pharmamatch retard with food and drink

The blood pressure lowering effect of nifedipine can be enhanced due to the intake of grapefruit juice. It is not recommended to drink grapefruit juice when treated with Nifedipine Pharmamatch retard.

It is recommended to take the Nifedipine Pharmamatch tablets in the morning with a glass of water (not grapefruit juice).

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

The safety of nifedipine during pregnancy has not been established. Nifedipine is contraindicated during pregnancy and not recommended in women who intend to get pregnant in the near future.

Breast-feeding

A small fraction of nifedipine passes into the breast milk. It is not known if this can lead to an effect in the infant. As a precaution, it is recommended to stop breast-feeding.

Driving and using machines

Nifedipine can cause dizziness, headache, fatigue or nausea, especially at the beginning of therapy, after a change in your medication or when consumed with alcohol. Therefore, the ability to drive or use machines can be reduced.

Important information about some of the ingredients of Nifedipine Pharmamatch retard

Nifedipine Pharmamatch retard contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

5. HOW TO TAKE NIFEDIPINE PHARMAMATCH RETARD

Dosage

Always take Nifedipine Pharmamatch retard exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual initial dose is one 30mg tablet once-daily. If necessary, your doctor can increase the dosage to 90 mg once-daily.

How to take

You should not chew or break the tablets. It is recommended to take the tablets in the morning with a glass of water (not grapefruit juice).

Duration of treatment

Your doctor will determine the duration of treatment. Do not stop the treatment early without consulting your doctor.

If you take more Nifedipine Pharmamatch retard than you should

If you take more Nifedipine Pharmamatch retard than you should, immediately contact your doctor or pharmacist. Elimination of the product and the restoration of stable cardiovascular conditions may be needed.

If you take too much nifedipine a low blood pressure (hypertension) can occur, which can be recognised from symptoms like dizziness, nausea, vomiting, drowsiness, confusion, lethargy, flushing, a lack of oxygen (hypoxia), headache or red spots on the face. Eventually, unconsciousness can occur. Increased or decreased heart rates are also a symptom of overdose.

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- headache
- flushing
- swelling, particularly of the ankles and legs

- giddiness
- light headedness
- feeling of pressure in the head.

Common (more than 1 out of 100, but less than 1 out of 10 patients):

- angina (upon sudden withdrawal of nifedipine)
- irregular heart beat (palpitations)
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- tiredness
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- increased frequency or worsening of angina
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Uncommon (more than 1 out of 1.000, but less than 1 out of 100 patients):

- heart rhythm disturbances
- increased sensitivity, particularly in arms and legs
- eye reactions such as eye pain, temporary vision disturbances
- finger twitching
- fever in the first few days after start of therapy
- transient increase in liver enzymes
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Rare (more than 1 out of 10.000, but less than 1 out of 1.000 patients):

- skin rash
- muscle cramps
- inflammation of the gums
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Very rare (Less than 1 out of 10.000 patients):

- bedwetting
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- blistering of the skin when exposed to sunlight (phototoxicity)
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