

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nifed Retard 10mg Modified Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg Nifedipine.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet

Round, slightly biconvex, pink film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nifed Retard 10 mg Modified Release Tablets are indicated for the treatment of mild to moderate hypertension and management of chronic stable angina pectoris.

4.2 Posology and method of administration

Route of administration: oral

Adults:

The recommended starting dose of Nifed Retard 10 mg Modified Release Tablets is 10 mg every 12 hours swallowed with water with subsequent titration of dosage according to response. The dose may be adjusted to 40 mg every 12 hours.

Nifed retard 10mg permits titration of initial dosage. The recommended dose is one Nifed retard 10mg tablet every 12 hours. The recommended dosage interval for Nifed retard 10mg tablets or retard 20mg tablets is about 12 hours and should not be less than 4 hours.

Tablets must be swallowed whole with a little liquid, independently of meals.

Nifed Retard should not be taken with grapefruit juice (see Section 4.5).

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see section 4.5).

The pharmacokinetics of nifedipine are altered in the elderly, so that lower maintenance doses may be required compared to younger patients.

Patients with renal impairment should not require adjustment of dosage.

Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored, and in severe cases, a dose reduction may be necessary.

Treatment may be continued indefinitely.

Children:

Nifed Retard 10 mg Modified Release Tablets are not recommended for treatment of children.

4.3 Contraindications

Nifed Retard 10 mg Modified Release Tablets should not be given to patients with known hypersensitivity to nifedipine or other tablet constituents or other dihydropyridines because of the theoretical risk of cross-reactivity.

It is contra-indicated during pregnancy and those breast-feeding their babies.

Nifed Retard 10mg should not be used in case of cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris or during or within one month of a myocardial infarction.

Nifed Retard 10mg should not be used for the treatment of acute attacks of angina.

Nifed Retard 10mg should not be used for secondary prevention after myocardial infarction.

The safety of Nifed Retard 10mg in malignant hypertension has not been established.

Nifed Retard 10mg should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.5)

4.4 Special warnings and precautions for use

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

Nifed Retard 10mg may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Nifedipine will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Nifed Retard 10mg should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Caution should be exercised in patients with severe hypotension.

Ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of nifedipine retard 10mg therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine.

Diabetic patients taking Nifed Retard may require adjustment of their control.

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

There are no safety and efficacy data from well-controlled studies in pregnant women (see section 4.6).

Animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects (see section 5.3) when administered during and after the period of organogenesis.

Whilst nifedipine is contra-indicated in pregnancy, particular care must be exercised when administering nifedipine in combination with i.v. magnesium sulphate to pregnant women.

Co-administration of nifedipine with erythromycin, ketoconazole, itraconazole, fluconazole, Fluoxetine, indinavir, nelfinavir, ritonavir, amprenavir and saquinavir may theoretically result in an increase in nifedipine plasma concentrations. Upon co-administration with any of these cytochrome P450 3A4 inhibitors, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (*See Sections 4.4. Special warnings and precautions for use*).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (*See Section 4.3. Contraindications*).

Upon co-administration of weak to moderate inhibitors of the cytochrome P450 3A4 system (listed immediately below), the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (*See Section 4.2 Posology and method of administration and see section 4.4. Special warnings and precautions for use*). 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): Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Azithromycin, although structurally related to the class of macrolide antibiotics is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors (e.g., ritonavir): Drugs of this class have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Azole anti-mycotics (e.g., ketoconazole): Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Fluoxetine: Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Nefazodone: Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase in nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Quinupristin/dalfopristin and cisapride: Simultaneous administration of quinupristin/dalfopristin and nifedipine, or cisapride and nifedipine, may lead to increased plasma concentrations of nifedipine (*See section 4.4. Special warnings and precautions for use*).

Valproic acid: As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker, nimodipine, due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded (*See section 4.4. Special warnings and precautions for use*).

Cimetidine: Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (*See section 4.4. Special warnings and precautions for use*).

Further studies

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

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

Effects of nifedipine on other drugs

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

- diuretics
- beta-blockers
- ACE-inhibitors
- AT-1 antagonists
- other calcium antagonists
- alpha-adrenergic blocking agents
- PDE5 inhibitors
- alpha-methyldopa

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

Digoxin: The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine: When nifedipine and quinidine have been administered simultaneously, lowered quinidine levels, or after discontinuation of nifedipine, a distinct increase in plasma concentrations of quinidine, have been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine.

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

Tacrolimus: Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Data recently published indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug food interactions

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice.

Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (*See Section 4.2. Posology and method of administration*).

Drugs shown not to interact with nifedipine

The following drugs have been shown to have no effect on the pharmacokinetics of nifedipine when administered concomitantly: ajmaline, aspirin, benazepril, candesartan cilexetil, debrisoquine, doxazosin, irbesartan, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone, talinolol and triamterene hydrochlorothiazide.

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Nifed Retard 10mg is contra-indicated during pregnancy. Nifed Retard 10mg should not be used by women who intend to get pregnant in the near future. The safety of Nifed Retard 10mg for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity consisting of embryotoxicity and teratogenic effects at maternally toxic doses.

Lactation:

Nifed Retard 10mg is contraindicated in breastfeeding. Nifedipine passes into breast milk, As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine becomes necessary during the breastfeeding period.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base; nifedipine n=2,661; placebo n=1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n=3,825; placebo n=3,840) are listed below: ADRs listed under 'common' were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%). ADRs derived from post marketing reports (status: 31 Mar 2006) are printed in *italics*

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $1/10$) , uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$),

very rare (<1/10,000), not known (cannot be estimated from the available data)

Immune system disorders

Uncommon: allergic reaction, allergic oedema/angioedema (incl. larynx oedema*)

Rare: pruritus, urticaria, rash

Very rare: *anaphylactic/anaphylactoid reaction*

Psychiatric disorders

Uncommon: anxiety reactions, sleep disorders

Nervous system disorders:

Common: headache

Uncommon: tremor, dizziness, migraine, vertigo

Rare: par - /dysaesthesia

Eye Disorders:

Uncommon: Visual disturbances

Cardiac disorders

Uncommon: tachycardia, palpitations

Vascular Disorders:

Common: Oedema Vasodilation

Uncommon: Hypotension, syncope

Respiratory, thoracic and mediastinal disorders

Uncommon: nasal congestion, nose bleed

Very rare: *Dyspnoea*

Gastro-intestinal Disorders:

Common: constipation

Uncommon: gastrointestinal and abdominal pain, nausea, flatulence, dry mouth, dyspepsia

Rare: Gingival hyperplasia

Very rare: *vomiting*

Hepatobiliary Disorders

Uncommon: Transient increase in liver enzymes

Musculoskeletal, connective tissue and bone disorders:

Uncommon: muscle cramps, joint swelling

Skin and subcutaneous tissue disorders:

Uncommon: erythema

Renal and Urinary Disorders:

Uncommon: Polyuria, dysuria

Reproductive System and Breast Disorders:

Uncommon: Erectile dysfunction

General Disorders and Administration Site Conditions:

Common: feeling unwell

Uncommon: 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

Symptoms

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

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac/bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Treatment

As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority.

After oral ingestion, thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Particularly in case of intoxication with slow release nifedipine formulations, such as Nifed Retard 10mg elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10-20 ml of a 10 % calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with beta-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm, temporary pacemaker therapy may be advisable.

Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO8CA05

Calcium channel blocker dihydropyridine derivative

Nifedipine is a specific and potent calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In hypertension, the main action of Nifed Regard 10mg is to cause peripheral vasodilatation and thus reduce peripheral resistance. In angina, Nifed Retard 10mg reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load.

Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Nifed retard 10mg administered twice daily provides 24 hours control of raised blood pressure.

Nifed retard 10mg causes reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Nifed retard 10mg has little or no effect on blood pressure.

5.2 Pharmacokinetic properties

Absorption:

After oral administration nifedipine is rapidly and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 – 56% owing to a first pass effect. Maximum plasma and serum concentration are reached at 1.5 to 4.2 hours with Nifed retard 20mg tablets. Simultaneous food intake leads to delayed, but not reduced absorption.

Distribution:

Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

Biotransformation

After oral administration nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites predominantly via the kidneys and about 5 – 15% via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1%) in the urine.

Elimination

The terminal elimination half-life is 6 – 11 hours (nifedipine retard), because of delayed absorption. No accumulation of the substance after the usual dose was reported during long-term treatment. In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers. In cases of impaired liver function the elimination half-life is distinctly prolonged and the total clearance is reduced. A dose reduction may be necessary in severe cases.

5.3 Preclinical safety data

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

Reproduction toxicology:

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration has been associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted fetuses (in rats, mice and rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Microcrystalline cellulose
Carboxymethyl sodium starch
Mannitol (E421)
Colloidal anhydrous silica
Povidone
Magnesium stearate
Sodium laurilsulfate

Tablet Coating

Hypromellose
Macrogol 6000
Macrogol 400
Red ferric oxide (E 172)
Titanium dioxide (E 171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package to protect from moisture and light.

Nifedipine is slightly sensitive to light and is therefore protected both by materials in the tablet and in the packaging. Nonetheless tablets should not be exposed to direct sunlight and should only be removed from the blister pack when about to be taken.

6.5 Nature and contents of container

Thermoformed blister packs of PVC/red transparent PVDC/aluminium in boxes of 14, 30, 56, 60 and 100 tablets.

Not all pack sizes may be marketed.

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

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/11/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 September 1999

Date of last renewal: 07 September 2009

10 DATE OF REVISION OF THE TEXT

February 2011