Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nifed Retard 20 mg modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains Nifedipine 20 mg.

Excipients: contains lactose monohydrate 9.8mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release film-coated tablet
Round, pink to light red biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of mild to moderate hypertension and for the management of chronic stable angina pectoris.

4.2 Posology and method of administration

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Route of Administration:

Oral.

Dosage regimen

As far as possible the treatment must be tailored to the needs of the individual according to the severity of the disease and the patient's response.

Depending on the clinical picture in each case, the basic dose must be introduced gradually.

Nifed retard 10mg is particularly suitable for dose titration. Dose titration is particularly recommended for hypertensives with severe cerebrovascular disease and for patients, who because of low body weight or multiple therapies with other antihypertensive drugs, are likely to have an excessive reaction to nifedipine. In addition, patients in whom side effects in response to the nifedipine treatment make a finer dose adjustment desirable should be individually stabilised with Nifed retard 10mg.

Unless otherwise prescribed, the following dosage guidelines apply for adults:

- In coronary heart disease:

Chronic stable angina pectoris (angina of effort)	1 Nifed retard 10mg tablet twice daily (2 x 10 mg/day) 1 Nifed retard 20mg tablet twice daily (2 x 20 mg/day)

If higher dosages are necessary, the dose can be increased in stages up to a maximum 60mg daily.

If there is no adequate therapeutic result after 14 days of treatment with Nifed retard a change over should be made to immediate release formulations (nifedipine capsules).

- In hypertension — 1 Nifed retard 10mg tablet twice daily (2 x 10mg/day)
  1 Nifed retard 20mg tablet twice daily (2 x 20mg/day)

If higher dosages are necessary, the dose can be increased in stages up to maximum 60mg daily.

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)

Duration of Treatment
The attending doctor will determine the duration of use.
Due to their pronounced antischemic and antihypertensive action, Nifed retard should be discontinued gradually, particularly when high doses are used.

Administration
As a rule Nifed retard tablets are swallowed whole with a little liquid irrespective of meal times. Grapefruit juice is to be avoided (see section 4.5)

The recommended dosage interval for Nifed retard tablets is about 12 h and should not be less than 4 h.

Additional information on special populations

Patients with hepatic impairment
In patients with impaired liver function, careful monitoring and, in severe cases, a dose reduction may be necessary.

Patients with renal impairment
Based on pharmacokinetic data no adjustment of dosage is required in patients with renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of nifedipine in children under the age 18 years have not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1.

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

4.3 Contraindications

NIFED should not be administered to patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross-reactivity.

Nifed should not be administered during pregnancy or to nursing mothers.

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

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

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

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

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

Caution should be exercised in patients with severe hypotension.

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

Ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of NIFED therapy. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue NIFED.
Diabetic patients taking Nifed 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 embrytoxic, 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

<u>Drugs that affect nifedipine.</u>

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 Section 4.4).*

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).*

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 Sections 4.2 and 4.4).* 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).*

Azithromycin, although structurally related to the class of macrolide antibiotics is void of CYP 3A4 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).*

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).*

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).*

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).*

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).*

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).*

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).*

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
-Angiotensin 1 (AT1) receptor-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 indicates 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.
Ginkgo biloba: Ginkgo biloba can increase levels and effects of nifedipine

I.V. Magnesium sulphate: 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.

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).*

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 is contra-indicated during pregnancy.

Nifed should not be used by women who intend to get pregnant in the near future.

The safety of Nifed 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 is contra-indicated in breastfeeding. Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

In-vitro fertilisation

In singe 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 consieder 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 the treatment, on changing the medication and in combination with alcohol.

4.8 Undesirable effects

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

The frequencies of ADRs reported with nifedipine containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and rare (≥1/10,000 to <1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under 'not known'

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				Agranulocytosis Leukopenia
Immune System Disorders		Allergic reaction Allergic oedema/angioedema	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction

		(incl. larynx oedema*)		
Psychiatric disorders		Anxiety reactions Sleep disorders		
Metabolism and nutrition disorders				Hyperglycaemia
Nervous System disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/dysaesthesia	Hypoasethesia Somnolence
Eye Disorders		Visual disturbances		Eye pain
Cardiac Disorders		Tachycardia Palpitations		Chest pain (angina pectoris)
Vascular Disorders	Oedema Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnoea
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastrooesophageal sphincter insufficiency
Hepatobiliary Disorders		Transient increase in liver enzymes		Jaundice
Skin and Subcutaneous Tissue disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal Connective Tissue and bone disorders		Muscle cramps Joint swelling		Anthralgia Myalgia Myasthenia gravis
Renal and Urinary Disorders		Polyuria Dysuria		
Reproductive System and breast disorders		Erectile dysfunction		
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		

*= may result in life threatening outcome.

In dialysis patients with malignant hypertension and hypovolaemia and 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.

Management of overdose
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 cases of intoxication with slow-release nifedipine formulations, such as Nifed retard, 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: Calcium channel blocker.
CO8CAO5: 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 is to cause peripheral vasodilatation and thus reduce peripheral resistance. In angina, Nifed 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 Modified-release tablets administered twice daily provides 24 hour control of raised blood pressure. NIFED Retard Modified-release tablets causes reduction in blood pressure such that the percentage lowering is directly related to its initial height. In normotensive individuals, Nifed has little or no effect on blood pressure.

In Raynaud's syndrome nifedipine can prevent or reduce the occurring digital vasospasm.

Paediatric population:
Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with different formulations in different dosages. Antihypertensive effects of nifedipine

have been demonstrated but dose recommendations, longterm safety and effect on cardiovascular outcome remain unestablished. Paediatric dosing forms are lacking.

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 nifedipine retard 20 mg 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 was determined to be 5 to 6 minutes.

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

Elimination
The terminal elimination half-life is 6 - 11 hours (nifedipin 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 was associated with a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, 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 fetotoxic effects in animals were maternally toxic at several times the recommended maximum dose for humans *(see Section 4.6)*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Polysorbate 80
Microcrystalline Cellulose
Magnesium Stearate
Hypromellose

Macrogol 4000
Titanium Dioxide (E171)
Red Ferric Oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

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

NIFED Retard 20 mg Modified-release Tablets are packed in blisters of polypropylene-aluminium and further packaged in outer cardboard cartons in units of 100 each.

Sample packs of 10 each of NIFED Retard 20mg Modified-release tablets are available. Hospital packs of 20 tablets of NIFED Retard 20mg Modified-release tablets are also available.

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 Limited
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/11/11

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 1990

Date of last renewal: 23 July 2010

10 DATE OF REVISION OF THE TEXT

March 2013