Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nifed 10mg soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Nifedipine 10.0 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft
Dark brown, oblong, soft gelatin capsule with a smooth shiny surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

NIFED is indicated for the treatment of essential hypertension. NIFED is also indicated for the management of chronic stable angina pectoris and the treatment of Raynaud's phenomenon.

For patients suffering from essential hypertension or chronic stable angina pectoris, and treated with fast release forms of nifedipine (Nifedipine 5mg and 10 mg capsules), a dose dependent increase in the risk of cardiovascular complications (e.g., myocardial infarction) and mortality may occur. Due to this, Nifedipine 5mg and 10 mg capsules should only be used for treatment of patients with essential hypertension or chronic stable angina pectoris if no other treatment is appropriate.

4.2 Posology and method of administration

Route of Administration

Oral.

Nifedipine should not be taken with grapefruit juice (see Interactions).

The capsules should be taken whole with a little liquid, independently of meals. The recommended starting dose is 5mg every eight hours with subsequent titration of dose according to response. The dose can be increased to a maximum of 20mg every eight hours. Patients taking 20mg unit doses of immediate release formulations should allow an interval of at least 2 hours between doses.

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 of nifedpine may be required compare to younger patients.

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.

Patients with renal impairment should not require adjustment of dosage.

Treatment may be continued indefinitely.

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

4.3 Contraindications

Nifed should not be administered to patients with known hypersensitivity to nifedipine or to other dihydropyridines because of the theoretical risk of cross-reactivity,or to any of the excipients,

Nifed should not be administered to women during pregnancy or to nursing mothers. (see section 4.4, 4.6 and 5.3)

NIFED should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina pectoris, or during or within 4 weeks of an acute 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 very low blood pressure (severe hypotension with systolic pressure less than 90mm Hg).

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 30 to 60 minutes of the introduction of NIFED therapy. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue NIFED.

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

Treatment with short acting Nifedipine may induce an exaggerated fall in blood pressure as well as reflex tachycardia, which cause cardiovascular complications such as myocardial and cerebrovascular ischaemia.

As with other vasoactive substances, angina pectoris may very rarely occur (data from spontaneous reports) with immediate release nifedipine, especially at the start of the treatment. Data from clinical studies confirm that the occurrence of angina pectoris attacks is uncommon.

In patients suffering from angina pectoris an increase in frequency, duration and severity of angina pectoris attacks may occur, especially at the start of the treatment.

The occurrence of myocardial infarction has been described in isolated cases, although it was not possible to

distinguish this from the natural course of the underlying disease.

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.

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

There is some concern about increased mortality and morbidity in the treatment of ischaemic heart disease, especially at higher dosages than those recommended, in particular after myocardial infarction.

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

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see section 4.5)

Drugs that are weak to moderate inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:

- macrolife antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- azole antimycotics (e.g. ketoconazole)
- the antidepressants, nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be 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*).

Ginkgo biloba: Ginkgo biloba can increase levels and effects of nifedipine.

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

Nifedipine is contra-indicated during pregnancy (see section 4.3)

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

The safety of nifedipine 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.

Nifedipine 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 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 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 (≥1/10), Common (≥1/100 to <1/10) , uncommon (≥1/1,000 to <1/100), rare (≥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, vertigo, migraine, dizziness

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*

Gastrointestinal disorders:
Common: Constipation
Uncommon: Gastrointestinal and abdominal pain, nausea, dry mouth, dyspepsia, flatulence
Rare: Gingival hyperplasia
Very rare:*vomiting.*

Hepatobiliary disorders
Uncommon: transient increase in liver enzymes

Skin and subcutaneous tissue disorders:
Uncommon: erythema

Musculoskeletal and connective tissue disorders:
Uncommon: muscle cramps, joint swelling
Unknown: potential for exacerbation of myasthenia gravis

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

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. In case of intoxication with nifedipine, 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
CO8CA05: dihydropyridine derivative

Nifedipine is a 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. As a specific and potent calcium antagonist, nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of NIFED is to relax arterial smooth muscle both in the coronary and peripheral circulation.

In angina pectoris, NIFED capsules relax peripheral arteries, so reducing the load on the left ventricle. Additionally NIFED dilates submaximally both clear and pre-stenotic, stenotic and post-stenotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

NIFED capsules reduce the frequency of painful attacks and ischaemic ECG changes, irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

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

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, long term safety and effect on cardiovascular outcome remain unestablished. Paediatric dosing forms are lacking.

5.2 Pharmacokinetic properties

Absorption
After oral administration nifedipine is immediately and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 - 56% owing to a first pass effect. Maximum plasma and serum concentrations are

reached at 30 to 60 minutes. 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 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 1.7 to 3.4 hours. 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 and several times the recommended maximum dose for humans (*See Section 4.6*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400
Glycerol
Saccharin Sodium
Menthol, racemic
Gelatin
Purified water
Ferric Oxide, red [E 172]
Ferric Oxide, black [E 172]
Ferric Oxide, yellow [E 172]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

NIFED 10 mg Capsules are packed in blisters of polypropylene-aluminium. NIFED 10 mg Capsules are available in pack sizes of 100 and sample packs of 10.

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 711/11/9

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

February 2013