Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adalat Retard 10 mg Prolonged-Release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated, prolonged-release tablet contains 10 mg nifedipine.

Excipients: Lactose monohydrate 10.00 mg per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated, prolonged-release tablets.
Grey-pink, circular tablets marked with A10 on one side and a Bayer cross on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Adalat retard 10 mg is intended primarily for the treatment of milder forms of cardiovascular diseases and in general, for those patients who, irrespective of the severity of their disease, respond particularly intensely to nifedipine. In addition Adalat retard 10 mg permits a gradual start to treatment and very finely adjusted dosage.

4.2 Posology and method of administration

Method of administration

Oral Use

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

Adalat retard 10 mg 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 stabilized with Adalat retard 10 mg.

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

- **In coronary heart disease:**

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

1 Adalat retard **20 mg** tablet twice daily
(2 x 20 mg/day)

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

If there is no adequate therapeutic result after 14 days of treatment with Adalat retard 10 mg or Adalat retard 20 mg a change over should be made to immediate release formulations (nifedipine capsules).

- In **hypertension:** **1** Adalat retard **10 mg** tablet twice daily
(2 x 10 mg/day)

1 Adalat retard **20 mg** tablet twice daily
(2 x 20 mg/day)

If higher dosages are necessary, the dose can be increased in stages up to maximum 60 mg 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 "Interaction with other medicinal products and other forms of interaction").*

Duration of Treatment

The attending doctor will determine the duration of use.

Due to their pronounced antischemic and antihypertensive action, Adalat retard should be discontinued gradually, particularly when high doses are used.

Administration

As a rule Adalat retard tablets are swallowed whole with a little liquid, irrespective of meal times. Grapefruit juice is to be avoided *(see, Interaction with other medicinal products and other forms of interaction").*

The recommended dosage interval for Adalat retard 10 mg or Adalat retard 20 mg is about 12 h and should not be less than 4 h.

Additional information on special populations

Paediatric populations

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

Elderly (>65) patients
The pharmacokinetics of Adalat retard are altered in the elderly so that lower maintenance doses of nifedipine may be required.

Patients with hepatic impairment
In patients with mild, moderate or severe impaired liver function, careful monitoring anda dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see "Special warnings and precautions for use" and "Pharmacokinetic properties").

Patients with renal impairment
Based on pharmacokinetic data no dosage adjustment is required in patients with renal impairment (*see "Pharmacokinetic properties"*)

The tablets must not be chewed or broken up!

4.3 Contraindications

Adalat retard 10 mg should not be administered to patients with known hypersensitivity to nifedipine or to other dihydropyridines because of the theoretical risk of cross-reactivity (see section 4.4, see section 6.1).

The safety of Adalat retard 10mg during pregnancy or in nursing mothers has not been established (see sections 4.4, 4.6 and 5.3).

Adalat retard 10 mg must 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.

Adalat retard 10 mg should not be used for the treatment of acute attacks of angina.

The safety of Adalat retard 10 mg in malignant hypertension has not been established.

Adalat retard 10 mg should not be used for secondary prevention of myocardial infarction.

Adalat retard 10 mg must 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

Adalat retard 10 mg 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.

Adalat retard 10 mg 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. Adalat retard 10 mg will not prevent possible rebound effects after cessation of other antihypertensive therapy.

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

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm HG), in cases of manifest heart failure and in the case of severe aortic stenosis.

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

Diabetic patients taking Adalat retard 10 mg may require adjustment of their control.

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

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.6).

Nifedipine is not recommended for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of oral absorption of small amounts of nifedipine are not known (see section 4.6).

Careful monitoring of blood pressure must be exercised, also when administered nifedipine with i.v. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and fetus.

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 hepatic impairment

In patients with mild, moderate or severe impaired liver function, careful monitoring anda dose reduction may be necessary (see section 5.2). The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see *"Dosage and method of administration"* and *"Pharmacokinetic properties"*). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

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

-macrolide 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.

For use in special populations see section 4.2.

Since this medicinal product contains lactose, 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

Drugs that affect nifedipine.
Nifedipine is metabolised via the cytochrome P450 3 A4 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):
No interaction studies have been carried out between nifedipine and macrolide antibiotics. 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):
A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. In addition, 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):
A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. 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:
A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. 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:
A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3 A4 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:
Simultaneous administration of quinupristin/dalfopristin and nifedipine, may lead to increased plasma concentrations of nifedipine *(see section 4.4)*.

Valproic acid:
No formal studies have been performed to investigate the potential interaction between nifedipine and 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
Cisapride
Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

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

-diuretics
-beta-blockers
-ACE-inhibitors
-Angiotensin II 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.

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 decrease 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

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.4).

Adalat Retard 10mg should not be used by women who intend to get pregnant in the near future.

The safety of Adalat retard 10 mg for use in human pregnancy has not been established.

There are no adequate and well controlled studies in pregnant women.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child.

In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity *(see section 5.3)*.

Evaluation of experimental animal studies has shown reproductive toxicity consisting of embryotoxicity and teratogenic effects at maternally toxic doses.

From the clinical evidence available a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean delivery as well as prematurity and intrauterine growth retardation has been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding
Nifedipine is excreted in the breast milk. The nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant (see section 4.4).

Fertility
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, can 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%).

The frequencies of ADRs reported with nifedipine containing products are summarized 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 (incl. larynx oedema [1])	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric Disorders		Anxiety reactions Sleep disorders		
Metabolism and nutrition disorders				Hyperglycaemia
Nervous System disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/ Dysaesthesia	Hypoaesthesia Somnolence
Eye Disorders		Visual disturbances		Eye pain
Cardiac Disorders		Tachycardia Palpitations		Chest pain (Angina pectoris)
Vascular Disorders	Oedema (incl. peripheral oedema) Vasodilation	Hypotension Syncope		
Respiratory, Thoracic, and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnea Pulmonary oedema*
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastrooesophageal sphincter insufficiency
Hepatobiliary		Transient		Jaundice

Disorders		increase in liver enzymes		
Skin and Subcutaneous Tissue Disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling		Arthralgia Myalgia
Renal and Urinary Disorders		Polyuria Dysuria		
Reproductive System and Breast Disorders		Erectile dysfunction		
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		

*cases have been reported when used as tocolytic during pregnancy (see section 4.6)
[[1]]=**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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

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 Adalat retard 10 mg and 20 mg, 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: C08 CA05

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 Adalat retard 10 mg is to cause peripheral vasodilatation and thus reduce peripheral resistance. In angina, Adalat retard 10 mg 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.

Adalat retard 10 mg administered twice-daily provides 24-hour control of raised blood pressure.

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

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

Paediatric populations:
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 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 Adalat 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 (Adalat 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 a non-blinded study among white subjects only (69% male), which compared the pharmacokinetics of single dose controlled-release nifedipine in patients with mild (Child Pugh A, n=8) or moderate (Child Pugh B, n=8) hepatic impairment with those in patients with normal liver function (n=8+8), oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and C_{max} of nifedipine increased on average by 93% (with 90% confidence interval 20.2%~ 209%) and 64% (with 90% confidence interval 14.3%~ 136%) for Child Pugh A, and by 253% (with 90% confidence interval 120%~ 466%) and 171% (with 90% confidence interval 88.7%~ 289%) for Child Pugh B, respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see *"Special warnings and precautions for use"*).

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

Microcrystalline cellulose
Maize starch
Lactose monohydrate
Polysorbate 80
Magnesium stearate

The tablet coating contains:
Hypromellose
Macrogol 4000
Ferric oxide red (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC blister packs: 48 months

PP blister packs: 30 months

6.4 Special precautions for storage

Keep container in the outer carton.

6.5 Nature and contents of container

Blister strips of tablets in a cardboard outer container, in packs of 56 tablets.

Blister strips are composed of red polypropylene foil 0.3 mm or red polyvinylchloride foil 0.25 mm, backed with aluminium foil.

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

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA1410/025/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 November 1987

Date of last renewal: 06 November 2007

10 DATE OF REVISION OF THE TEXT

September 2016