Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adalat LA 30 mg Prolonged-Release Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 30 mg nifedipine.

Excipients with known effect
Each tablet contains 9.4 mg sodium. Please see section 4.4 for further information.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release film-coated tablet.

Pink, circular convex tablets with Adalat 30 marked on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of all grades of hypertension.

For the management of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker.

4.2 Posology and method of administration

Posology

As far as possible the treatment must be tailored to the needs of the individual.

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

Unless otherwise prescribed, the following dosage guidelines are recommended for adults:

- For **coronary heart disease: Chronicstable angina pectoris**(angina of effort)1 Adalat LA 30 mg tablet once daily (1 x 30 mg/day)
- For **hypertension:**1 Adalat LA 30 mg tablet once daily (1 x 30 mg/day)

In general therapy should be initiated with 30 mg once daily.
Where registered a starting dose of 20 mg once daily may be considered when medically indicated. Interim doses i.e. 40 mg, 50 mg etc. can be applied by combinations of i.e. 20 mg + 20 mg or 20 mg + 30 mg tablets.

Depending on the severity of the disease and the patient's response the dose can be increased in stages up to 90 mg once 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 other forms of interaction")*.

Duration of Treatment
The attending doctor will determine the duration of use.

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

Based on pharmacokinetic data for Adalat LA no dose adaptation in elderly people above 65 years is necessary.

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 dosage adjustment is required in patients with renal impairment (*see "pharmacokinetic properties"*).

Method of Administration

As a rule Adalat LA tablets are swallowed whole with a little liquid, irrespective of meal times.Grapefruit juice is to be avoided *(see Section 4.5).*

The coated tablet should not be broken or chewed, as the coating is intended to ensure a prolonged release (see Section 5.2).

4.3 Contraindications

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

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

Adalat LA must not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

Adalat LA must not be used for the treatment of acute attacks of angina.

The safety of Adalat LA in malignant hypertension has not been established.

Adalat LA must not be used for secondary prevention of myocardial infarction.

Owing to the duration of action of the formulation, Adalat LA must not be administered to patients with hepatic impairment.

Adalat LA must not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.

Adalat LA must not be used in patients with Kock pouch (ileostomy after proctocolectomy)

Adalat LA is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.

Adalat LA 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 LA tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

The outer membrane of the Adalat LA tablet is not digested and, therefore, what appears to be the complete tablet may be seen in the toilet or associated with the patient's stools.

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.

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

Adalat LA 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 LA will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Adalat LA 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 following the introduction of nifedipine therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

Diabetic patients taking Adalat LA 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 pressurewhich 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).

As the outer membrane of the Adalat LA tablet is not digested, care should be exercised as obstructive symptoms may occur, particularly in patients with pre-existing severe gastrointestinal narrowing. Bezoars can occur in very rare cases and may require surgical intervention.

In single cases obstructive symptoms have been described without known history of gastrointestinal disorders.

Adalat LA must not be administered to patients with Kock pouch (ileostomy after proctocolectomy).

A false positive effect may be experienced when performing a barium contrast x-ray.

Patients with hepatic impairment
In patients with impaired liver function, careful monitoring and, in severe cases, a dose reduction may be necessary (see section 5.2).

This medicinal product contains 9.4mg sodium per dose; this should be taken into consideration for patients on a controlled sodium diet.

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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interactions

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 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 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
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).

Diltiazem:
Diltiazem decreases the clearance of nifedipine and, hence, increases plasma nifedipine levels. Therefore, caution should be taken when both drugs are used in combination and a reduction of the nifedipine dose may be necessary.

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 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 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 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).

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

The safety of Adalat LA 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 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 (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**	**Hypotension** Syncope		

	oedema) Vasodilatation			
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	**Bezoar** **Dysphagia** **Intestinal obstruction** **Intestinal ulcer** **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 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 Website: www.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 products like Adalat LA, 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 solely by the patient's response.

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

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives.

ATC code: C08 CA05

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 nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Adalat LA tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.

In hypertension, the main action of nifedipine is to cause peripheral vasodilatation and thus reduce peripheral resistance. Nifedipine administered once-daily provides 24-hour control of raised blood pressure. Nifedipine causes reduction in blood pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect on blood pressure.

In angina, Adalat LA 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.

In multi-national, randomised, double-blind, prospective study involving 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, Adalat LA 30 and 60 (nifedipine GITS) were shown to reduce cardiovascular and cerebrovascular events to a comparable degree as a standard diuretic combination.

In the multicentre, randomized, placebo-controlled, double-blind ACTION trial with a follow-up of 5 years involving 7665 patients with stable angina pectoris on best practice standard treatment the effects on clinical outcomes of nifedipine LA vs placebo were investigated.

The primary endpoint for efficacy (combined rate of death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularization) did not differ between patients assigned nifedipine LA (n=3825) and patients allocated placebo (n=3840) (P=0.54).

In a predefined subgroup analysis which included 3997 angina patients with hypertension at baseline nifedipine LA led to a significant 13% reduction of the primary endpoint for efficacy.

Nifedipine LA has been demonstrated to be safe as the primary endpoint for safety (combined rate of death from any cause, acute myocardial infarction, and debilitating stroke) was similar in both treatment groups (P=0.86).

Nifedipine LA had a positive effect on two of the three predefined secondary endpoints. The combined rate of death, major cardiovascular events, revascularization, and coronary angiography (CAG) was reduced by 11% (p=0.0012), the main reason being the pronounced reduction in the need for coronary angiography. There were 150 fewer CAGs as the first event in the nifedipine group when compared to placebo. Any vascular event was reduced by 9% (p=0.027), the main reason being the reduced need for percutaneous coronary interventions and bypass surgery. In total, there were 89 fewer procedures as first events in the nifedipine group compared to placebo. The outcome of the third secondary endpoint 'major cardiovascular event' did not show differences between the two treatment groups (P=0.26).

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

General characteristics:

Adalat LA tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0-24 hour plasma concentration versus time profiles at steady-state are plateau-like, rendering the Adalat LA tablet appropriate for once-a-day administration.

The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45-56% owing to a first pass effect. At steady-state, the bioavailability of Adalat LA tablets ranges from 68-86% relative to Adalat capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

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 eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5-15% being excreted via the bile in the faeces. Non-metabolised nifedipine can be detected only in traces (below 1.0%) in the urine.

Elimination

The terminal elimination half-life is 1.7 to 3.4h in conventional formulations (nifedipine capsules). The terminal half-life following Adalat LA administration does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption.

Characteristics in patients:

There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.

In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. Owing to the duration of action of the formulation, Adalat LA should not be administered in these patients.

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.

Following acute oral and intravenous administration of nifedipine in various animal species, the following LD50 (mg/kg) values were obtained:

Mouse:	Oral: 494 (421-572)*;	i.v.: 4.2 (3.8-4.6)*.
Rat:	Oral: 1022 (950-1087)*;	i.v.: 15.5 (13.7-17.5)*.
Rabbit:	Oral: 250-500;	i.v.: 2-3.
Cat:	Oral: ~ 100;	i.v.: 0.5-8.
Dog:	Oral: > 250;	i.v.: 2-3.

* 95% confidence interval.

In subacute and subchronic toxicity studies in rats and dogs, nifedipine was tolerated without damage at doses of up to 50 mg/kg (rats) and 100 mg/kg (dogs) p.o. over periods of thirteen and four weeks, respectively. Following intravenous administration, dogs tolerated up to 0.1 mg/kg nifedipine for six days without damage. Rats tolerated daily intravenous administration of 2.5 mg/kg nifedipine over a period of three weeks without damage.

In chronic toxicity studies in dogs with treatment lasting up to one year, nifedipine was tolerated without damage at doses up to and including 100 mg/kg p.o. In rats, toxic effects occurred at concentrations above 100 ppm in the feed (approximately 5-7 mg/kg bodyweight).

In a carcinogenicity study in rats (two years), there was no evidence of a carcinogenic effect of nifedipine.
Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palate 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.
In *in vitro* and *in vivo* tests, nifedipine has not been associated with mutagenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Polyethylene oxide
Hypromellose
Magnesium stearate

Osmotic Blend
Polyethylene oxide
Sodium chloride
Hypromellose
Ferric oxide, red (E172)
Magnesium stearate

Organic Coating
Cellulose acetate
Macrogol 3350

Light Protective Coating
Hydroxypropylcellulose
Hypromellose
Propylene glycol
Titanium dioxide (E171)
Ferric oxide, red (E172)

Polish
Hypromellose

Printing ink
Black ink Opacode S-1-17823
{contains: Iron oxide black (E172), Shellac and Propylene glycol (E1520)}

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Polypropylene/ aluminium foil blister packs: 4 years
Polyvinyl chloride/ polyvinylidene chloride/ aluminium foil blister packs: 3 years

6.4 Special precautions for storage

Store in the original container. The tablets should be protected from strong light. Do not store above 30°C.

6.5 Nature and contents of container

Polypropylene/ aluminium foil - or polyvinyl chloride/polyvinylidene chloride/ aluminium foil - blister packs, containing 28 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1410/025/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th April 1994
Date of last renewal: 30th October 2007

10 DATE OF REVISION OF THE TEXT

November 2020