

DATA SHEET

ADALAT[®] OROS

nifedipine

Name of Medicine

Adalat OROS (nifedipine) extended release tablets

Presentation

Each Adalat OROS 30 extended release tablet contains 30 mg nifedipine
Each Adalat OROS 60 extended release tablet contains 60 mg nifedipine

Round, convex extended release tablet, with pink coat, laser hole on one side.

Excipients

Each Adalat OROS 30 extended release tablet contains 23.9 mg sodium chloride
Each Adalat OROS 60 extended release tablet contains 47.8 mg sodium chloride

For a full list of excipients, see List of Excipients.

Clinical Particulars

Indications

- Treatment of coronary heart disease
Chronic stable angina pectoris (angina of effort)
- Treatment of hypertension

Dosage and Method of Administration

Dosage regimen

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. 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:
Chronic stable angina pectoris One Adalat OROS 30 tablet once daily

(angina of effort) (1 x 30 mg/day)
One Adalat OROS 60 tablet once daily
(1 x 60 mg/day)

For hypertension: One Adalat OROS 30 tablet once daily
(1 x 30 mg/day)
One Adalat OROS 60 tablet once daily
(1 x 60 mg/day)

In general, therapy should be initiated with 30 mg once daily.

Coadministration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the Adalat OROS dose or not to use Adalat OROS at all (see **Interactions with Other Medicinal Products or Other Forms of Interaction**).

Duration of Treatment

The attending doctor will determine the duration of use.

Method of Administration

As a rule the 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 tablets must not be chewed or broken up!

Additional information on special populations

Children and adolescents

The safety and efficacy of Adalat OROS in children below 18 years has not been established.

Geriatric patients

Based on the pharmacokinetic data for Adalat OROS, 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**).

Contraindications

Adalat OROS must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients (see **List of Excipients**).

Adalat OROS is contraindicated in pregnancy before week 20 and during breastfeeding (see **Pregnancy and Lactation**).

Adalat OROS must not be used in cases of cardiovascular shock.

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

Adalat OROS must not be used in combination with rifampicin because efficient plasma levels of nifedipine may not be obtained due to enzyme induction (see **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Special Warnings and Precautions for Use

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

There are no safety and efficacy data from well-controlled studies in pregnant women.

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

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

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy after week 20 requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

Careful monitoring of blood pressure must be exercised, also when administering Adalat OROS with intravenous magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and fetus.

As with other non-deformable material (see **Instructions for Use/Handling**) care should be used when administering Adalat OROS in patients with pre-existing severe gastrointestinal narrowing because obstructive symptoms may occur. 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.

When doing barium contrast X-ray, Adalat OROS may cause false positive effects (e.g. filling defects interpreted as polyp).

In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary (see **Pharmacokinetic Properties**).

Adalat OROS modified release tablets are not bioequivalent to immediate release nifedipine capsules and tablets. Patients should be carefully monitored if it is decided to switch between immediate release and modified release nifedipine or vice versa.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass

or the clearance of nifedipine (see **Interaction with Other Medicinal Products and Other Forms of Interaction**).

Medicines, which are inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine, are, e.g.:

- 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 medicines, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Dose titration up to the maximal daily dose of 120 mg nifedipine may result in a maximal uptake of (2 mmol sodium) per day. This should be taken into consideration for patients on a controlled sodium diet.

For use in special populations, see **Dosage and Method of Administration**.

Interaction with Other Medicinal Products and Other Forms of Interaction

Medicines that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the intestinal mucosa and in the liver. Medicines 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 **Special Warnings and Precautions for Use**).

The extent as well as the duration of interactions should be taken into account when administering Adalat OROS together with the following medicines:

Rifampicin

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

Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the Adalat OROS dose considered (see **Dosage and Method of Administration**).

Macrolide antibiotics (e.g. erythromycin)

No interaction studies have been carried out between Adalat OROS and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore the potential for an increase

of nifedipine plasma concentrations with co-administration of both medicines cannot be excluded (see **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)

A clinical study investigating the potential of a drug interaction between Adalat OROS and certain anti-HIV protease inhibitors has not yet been performed. Medicines of this class are known to inhibit the cytochrome P450 3A4 system. In addition, medicines of this class have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with Adalat OROS, a substantial increase in plasma concentration of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded (see **Special Warnings and Precautions for Use**).

Azole anti-mycotics (e.g., ketoconazole)

A formal interaction study investigating the potential of a drug interaction between Adalat OROS and certain azole anti-mycotics has not yet been performed. Medicines of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with Adalat OROS, a substantial increase in systemic bioavailability of nifedipine due to an increased absorption cannot be excluded (see **Special Warnings and Precautions for Use**).

Fluoxetine

A clinical study investigating the potential of a drug interaction between Adalat OROS and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded (see **Special Warnings and Precautions for Use**).

Nefazodone

A clinical study investigating the potential of a drug interaction between Adalat OROS and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded (see **Special Warnings and Precautions for Use**).

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and Adalat OROS may lead to increased plasma concentrations of nifedipine, with the effect varying markedly between individuals (see **Special Warnings and Precautions for Use**).

Valproic Acid

No formal studies have been performed to investigate the potential interaction between Adalat OROS 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 **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 **Special Warnings and Precautions for Use**).

Further studies

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

Cytochrome P450 3A4 system-inducing anti-epileptic medicines, such as phenytoin, carbamazepine and phenobarbitone

A formal interaction study investigating the potential of a drug interaction between nifedipine and phenytoin has not yet been performed. However, phenytoin is known as a potential inducer of the cytochrome P450 3A4 system. Furthermore, concomitant administration of phenytoin and drugs structurally related to nifedipine clearly reduced their bioavailability. Thus a clinically relevant reduction of the bioavailability of nifedipine cannot be excluded.

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy is weakened. When both medicines are concomitantly administered, the clinical response to Adalat OROS should be monitored and, if necessary, an increase of the Adalat OROS dose considered. If the dose of Adalat OROS is increased during co-administration of both medicines, a reduction of the Adalat OROS 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 phenobarbitone. As both medicines 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 medicines

Blood pressure lowering medicines

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

- diuretics,
- β -blockers,
- ACE-inhibitors,
- angiotensin 1 (AT1) receptor-antagonists,
- other calcium antagonists,
- α -adrenergic blocking agents,
- PDE5 inhibitors,
- α -methyldopa.

When Adalat OROS is administered simultaneously with β -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 Adalat OROS and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin. Therefore, as a precaution therefore the patient should be checked for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine

When Adalat OROS and quinidine have been administered simultaneously, occasionally lowered quinidine plasma concentrations have been observed in individual cases. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of nifedipine. Also in some cases after the discontinuation of nifedipine a distinct increase in plasma concentrations of quinidine have been noted. 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 is recommended.

Diltiazem

Diltiazem decreases the clearance of nifedipine. The combination of both medicines should be administered with caution and a reduction of the Adalat OROS dose may be considered.

Tacrolimus

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

Interactions with other medicinal products

The blood pressure lowering effect of Adalat OROS may be potentiated with co-administration of other antihypertensive medicines.

Drug-food Interactions

Grapefruit Juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of Adalat OROS together with grapefruit juice results in elevated plasma concentrations and prolonged action of nifedipine due to an increase of drug bioavailability. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice, this effect may last for at least 3 days after the last ingestion of grapefruit juice.

Ingestion of grapefruit / grapefruit juice should therefore to be avoided while taking Adalat OROS (see **Dosage and Method of Administration**).

Interactions Shown not to Exist

Ajmaline

Concomitant administration of nifedipine and ajmaline has no effect on the metabolism of ajmaline.

Aspirin

Concomitant administration of nifedipine and aspirin 100 mg has no effect on the pharmacokinetics of nifedipine. Co-administration of nifedipine does not alter the effect of aspirin 100 mg on the platelet aggregation and bleeding time.

Benazepril

Concomitant administration of nifedipine and benazepril has no effect on the pharmacokinetics of nifedipine.

Candesartan Cilexetil

Concomitant administration of nifedipine and candesartan cilexetil has no effect on the pharmacokinetics of either medicine.

Debrisoquine

Concomitant administration of nifedipine and debrisoquine has no effect on the metabolic ratio of debrisoquine.

Doxazosin

Concomitant administration of nifedipine and doxazosin has no effect on the pharmacokinetics of nifedipine.

Irbesartan

Concomitant administration of nifedipine and irbesartan has no effect on the pharmacokinetics of irbesartan.

Omeprazole

Concomitant administration of nifedipine and omeprazole has no clinically relevant effect on the pharmacokinetics of nifedipine.

Orlistat

Concomitant administration of nifedipine and orlistat has no effect on the pharmacokinetics of nifedipine.

Pantoprazole

Concomitant administration of nifedipine and pantoprazole has no effect on the pharmacokinetics of nifedipine.

Ranitidine

Concomitant administration of nifedipine and ranitidine has no effect on the pharmacokinetics of nifedipine.

Rosiglitazone

Concomitant administration of nifedipine and rosiglitazone has no clinically relevant effect on the pharmacokinetics of nifedipine.

Talinolol

Concomitant administration of nifedipine and talinolol has no effect on the pharmacokinetics of nifedipine.

Triamterene Hydrochlorothiazide

Concomitant administration of nifedipine and triamterene hydrochlorothiazide has no effect on the pharmacokinetics of nifedipine

Other forms of interaction

Nifedipine may cause falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

Pregnancy and Lactation

Pregnancy

Adalat OROS is contraindicated in pregnancy before week 20 (see **Contraindications**).

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

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 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 under developed 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 vitro* Fertilisation**

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.

Lactation

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.

Effect on Ability to Drive and Use Machines

Reactions to the medicine, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery (see **Undesirable Effects**). This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

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 = 2661; placebo n = 1486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3825; placebo n = 3840) 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 Table 1 below. With each frequency grouping, ADRs are presented in order of decreasing seriousness.

The frequencies of ADRs are defined as:
 Common $\geq 1/100$ to $< 1/10$ ($\geq 1\%$ to $<10\%$)
 Uncommon $\geq 1/1000$ to $< 1/100$ ($\geq 0.1\%$ to $<1\%$)
 Rare $\geq 1/10000$ to $< 1/1000$ ($\geq 0.01\%$ to $<0.1\%$)

Table 1. Adverse Drug Reactions reported based on clinical trial data

Clinical Description	Common $\geq 1\%$ to $<10\%$	Uncommon $\geq 0.1\%$ to $<1\%$	Rare $\geq 0.01\%$ to $<0.1\%$
Immune System Disorders			
Acute Hypersensitivity reactions		Allergic reaction Allergic oedema / angioedema (including larynx oedema*)	Pruritus Urticaria Rash
Psychiatric Disorders			
Behavioural disturbances and sleep disorders		Anxiety reactions Sleep disorders	
Nervous System Disorders			
Unspecific cerebro-vascular symptoms	Headache	Vertigo Migraine	
Unspecific neurological symptoms		Dizziness Tremor	
Unspecific altered peripheral perception			Par-/Dysaesthesia
Eye Disorders			
Unspecific eye disorders		Visual disturbances	
Cardiac Disorders			
Unspecific arrhythmias		Tachycardia Palpitations	
Vascular Disorders			
Unspecific vascular symptoms	Oedema Vasodilatation	Hypotension Syncope	
Respiratory, Thoracic, and Mediastinal Disorders			

Clinical Description	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Upper respiratory tract symptoms		Nosebleed Nasal congestion	
Gastrointestinal Disorders			
Gastro-intestinal symptoms	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia
Hepatobiliary Disorders			
Mild to moderate hepatic reactions		Transient increase in liver enzymes	
Skin and Subcutaneous Tissue Disorders			
Unspecific skin reactions		Erythema	
Musculoskeletal and Connective Tissue Disorders			
Unspecific joint and muscular disorders		Muscle cramps Joint swelling	
Renal and Urinary Disorders			
Urinary disorders		Polyuria Dysuria	
Reproductive System Disorders			
Sexual dysfunction		Erectile dysfunction	
General Disorders and Administration Site Conditions			
General feeling of illness	Feeling unwell	Unspecific pain Chills	

* = may result in life-threatening outcome

In dialysis patients with malignant hypertension and hypovolaemia, a distinct fall in blood pressure can occur as a result of vasodilation.

The most common adverse effect reported was oedema which was dose-related and ranged in frequency from approximately 10% on 30 mg to 30% at the highest dose studied (180 mg).

Post marketing adverse effects

The ADRs identified during the ongoing market surveillance and for which a frequency could be not estimated are: agranulocytosis, leukopaenia, anaphylactic/anaphylactoid reaction, hyperglycaemia, hypoaesthesia, somnolence,

eye pain, chest pain (angina pectoris), dyspnoea, bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting, gastroesophageal sphincter insufficiency, jaundice, toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura, arthralgia and myalgia.

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 OROS 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).

Bradycardiac heart rhythm disturbances may be treated symptomatically with β -sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10 to 20 mL of a 10 % calcium gluconate solution administered slowly intravenously 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 are additionally administered. The dosage of these medicines is determined solely by the effect obtained.

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

Pharmacodynamic Properties

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. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In the heart nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of partially stenosed areas. Further, nifedipine reduces the vascular smooth muscle tone in the coronary arteries and prevents vasospasm. The end-result is an increased poststenotic blood flow and an increased oxygen supply. Parallel to this, nifedipine reduces the oxygen requirement by lowering peripheral resistance (afterload). With long-term use nifedipine can also prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine reduces the smooth muscle tone of the arterioles, thus lowering the increased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex increase in heart rate and thus in the cardiac output. However, this increase is not enough to compensate for the vasodilation. In addition nifedipine increases sodium and water excretion both in the short-term and long-term use. The blood-pressure-lowering effect of nifedipine is particularly pronounced in hypertensive patients.

In the multicenter, randomised, 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 Adalat OROS 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 revascularisation) did not differ between patients assigned Adalat OROS (n=3825) and patients allocated placebo (n=3 840) ($P=0.54$).

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

Adalat OROS 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 ($P=0.86$).

Adalat OROS had a positive effect on two of the three predefined secondary endpoints. The combined rate of death, major cardiovascular events, revascularisation, 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 Adalat OROS 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 Adalat OROS group compared to placebo. The outcome of the third secondary endpoint 'major cardiovascular event' did not show differences between the two treatment groups ($P=0.26$).

Pharmacokinetic Properties

Adalat OROS 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 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

After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations (Adalat capsules) is 45 to 56 % owing to a first pass effect. At steady-state the bioavailability of Adalat OROS tablets ranges from 68 to 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.

Plasma drug concentrations rise at a controlled rate after Adalat OROS dose and reach a plateau at approximately 6 to 12 hours after the first dose. Following multiple days of dosing, relatively constant plasma concentrations at this niveau are maintained with minimum peak to trough fluctuations over a 24 hours dosing interval (0.9 to 1.2 ng/mL).

Table 2 shows the peak plasma concentrations (C_{max}) of Adalat OROS tablets and the time to reach the peak plasma concentrations (t_{max}):

Table 2. Peak plasma concentrations and time to reach peak plasma concentrations

	C_{max} (ng/mL)	t_{max} (h)
Adalat OROS 30 mg extended release tablet	20 – 21	12 - 15 *
Adalat OROS 60 mg extended release tablet	43 – 55	7 - 9 *

* not pronounced due to plateau - like plasma concentration time course

Distribution

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

Biotransformation

After oral administration nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity.

Nifedipine is excreted in the form of its metabolites predominantly via the kidneys, and about 5 to 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 in conventional formulations (Adalat capsules). The terminal half-life after Adalat OROS does not represent a meaningful parameter as a plateau- like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of last dose, the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

In cases of impaired kidney function, no substantial changes have been detected in comparison with healthy volunteers.

In cases of impaired liver function, the total clearance is reduced. A dose reduction may be necessary in severe cases (see **Special Warnings and Precautions for Use**).

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.

Acute toxicity

Acute toxicity has been investigated in various animal species and the individual results are listed in Table 3:

Table 3. Acute toxicity in various animal species

	LD ₅₀ (mg/kg)	
	Oral	Intravenous
Mouse	494 (421 - 572)*	4.2 (3.8 - 4.6)*
Rat	1022 (950 - 1087)*	15.5 (13.7-17.5)*
Rabbit	250 - 500	2 - 3
Cat	~100	0.5 - 8
Dog	>250	2 - 3

* 95 % confidence level

Subacute and subchronic toxicity

Daily oral administration to rats (50 mg/kg body weight) and to dogs (100 mg/kg body weight) over periods of 13 and 4 weeks respectively were tolerated without toxic effects.

After parenteral (intravenous) administration, dogs tolerated up to 0.1 mg/kg body weight/day for 6 days without damage. Daily intravenous administration of 2.5 mg/kg body weight in rats over a period of 3 weeks was also tolerated without signs of damage.

Chronic toxicity

Dogs tolerated up to 100 mg/kg body weight as a daily oral dose over a period of 1 year without toxic effects. In rats, toxic effects occurred at concentrations above 100 ppm in the feed (about 5 to 7 mg/kg body weight).

Carcinogenicity

A long-term study in rats (2 years) yielded no evidence of a carcinogenic effect of nifedipine.

Mutagenicity

To assess the mutagenic effects the Ames test, the Dominant-lethal-test, and the Micronucleus-test were performed in the mouse. No evidence of a mutagenic effect of nifedipine could be found.

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 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.

Pharmaceutical Particulars

List of Excipients

Hypromellose
Polyethylene oxide
Magnesium stearate
Sodium chloride
Iron oxide red (E 172/C.I.77491)
Cellulose acetate
Macrogol 3350
Hydroxypropyl cellulose
Propylene glycol
Titanium dioxide (E171/C.I.77891)

Incompatibilities

None

Shelf-life

48 months, stored below 30°C.

Special Precautions for Storage

None

Nature and Contents of Container

Blister pack PVC/Aclar	-	30's
Bottle, plastic HDPE	-	30's
Blister pack PVC/PVDC	-	30's

Instructions for Use/Handling

In Adalat OROS, the medication is contained within a non-absorbable shell that slowly releases the medicine for the body to absorb. When this process is completed, the empty tablet is eliminated from the body and may be noticed in the stool.

The light-sensitive active substance contained in Adalat OROS is protected from light inside and outside its packaging. The tablets must be protected from humidity and must therefore only be removed from the foil immediately before use.

Medicine Classification

Prescription Medicine

Name and Address

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free Phone: 0800 233 988

Date of Preparation

07 April 2010

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