Information for Healthcare Professionals

1. NAME OF THE MEDICINAL PRODUCTS

Adalat® LA 30 mg, prolonged-release tablets
Adalat® LA 60 mg, prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Adalat LA 30 mg:
1 prolonged-release tablet contains 30 mg nifedipine.

Adalat LA 60 mg:
1 prolonged-release tablet contains 60 mg nifedipine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Adalat LA 30 mg, prolonged-release tablets: pink, round, convex prolonged-release tablets with a laser hole, marked with "Adalat 30" on one side.

Adalat LA 60 mg, prolonged-release tablets: pink, round, convex prolonged-release tablets with a laser hole, marked with "Adalat 60" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of essential hypertension.

4.2 Posology and method of administration

Posology

The following dosage guidelines apply for adults:
The target dose is 1 Adalat LA 30 mg prolonged-release tablet once daily (equivalent to 30 mg nifedipine once daily).
If needed, the dose can be increased to 1 Adalat LA 60 mg prolonged-release tablet once daily or 2 Adalat LA 30 mg prolonged-release tablets once daily (equivalent to 60 mg nifedipine once daily).
When co-administering agents that inhibit or induce the cytochrome P450 3A4 system, it may be necessary to adjust the nifedipine dose or, if necessary, to withhold the use of nifedipine completely (see section 4.5).

Note
Adalat LA 30/60 mg contains a tablet shell which is excreted with the faeces after release of the active substance.

Additional information on certain patient groups

Paediatric population
Adalat LA 30/60 mg is not intended for use in children and adolescents below 18 years of age due to the lack of experience. Currently available data on the use of nifedipine in hypertension are described in section 5.1.

Elderly patients (> 65 years)
Based on the pharmacokinetic data, no dose adjustment is needed in elderly patients (> 65 years).

Patients with impaired hepatic function
In patients with mild, moderate or severe impaired liver function careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4 and section 5.2).

Patients with impaired renal function
Based on the pharmacokinetic data, no dose adjustment is needed in patients with impaired renal function (see section 5.1).

Method of administration

Oral use

Adalat LA 30/60 mg prolonged-release tablets are taken with sufficient liquid (e.g. a glass of water), preferably always at the same time of day. The prolonged-release tablets must not be chewed or divided. Adalat LA 30/60 mg must not be taken with grapefruit juice (see section 4.5).
The prolonged-release tablets can be taken independently of meals.

The duration of use is decided by the treating physician.

4.3 Contraindications

Adalat LA 30/60 mg must not be taken in the following cases:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- cardiovascular shock
- higher-grade aortic stenosis
- unstable angina pectoris
- acute myocardial infarction (within the first 4 weeks)
- severe stenosis of the gastrointestinal tract lumen
- ileostomy (post proctocolectomy) or colostomy
- concomitant treatment with rifampicin, as no effective nifedipine plasma levels will be reached due to enzyme induction (see section 4.5)
- during pregnancy before week 20 and during breast-feeding (see section 4.6).

Adalat LA 30/60 mg is not intended for use in children and adolescents under 18 years of age, due to the lack of experience.

4.4 Special warnings and precautions for use

Particularly careful medical surveillance is required in the following cases:
- severe hypotension (RR values less than 90 mmHg systolic)
- congestive heart failure
- dialysis patients with malignant hypertension and hypovolaemia (a significant decrease in blood pressure may occur as a result of vasodilation)
- pregnancy (see sections 4.3 and 4.6).

As with other non-deformable materials, Adalat LA 30/60 mg should be used with caution in patients with pre-existing stenosis in the gastrointestinal tract, as obstructive symptoms may occur. Bezoar stones (gastroliths) have been observed in very rare cases, necessitating surgical intervention.
In individual cases, symptoms of intestinal obstruction have been described, without any known history of gastrointestinal disease.
If diarrhoea persists for several days (e.g. in Crohn's disease, inflammatory bowel disease), absorption of the active substance may be incomplete, as the drug residence time within the gastrointestinal tract is too short.

In X-ray examinations with contrast agents, Adalat LA 30/60 mg prolonged-release tablet shells within the gastrointestinal tract may become visible on the X-ray image and produce false-positive findings (e.g. filling defect interpreted as polyps).

In patients with mild, moderate or severe impaired liver function careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.2 and section 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Thus, active substances known to influence this enzyme system can alter the first-pass metabolism or excretion of nifedipine (see section 4.5).

The plasma levels of nifedipine can, for example, be increased by the following medicinal products known to be inhibitors of this enzyme system:
- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- antifungals of the azole type (e.g. ketoconazole)
- antidepressants: nefazodone and fluoxetine
- quinupristin / dalfopristin
- valproic acid
- cimetidine
- tricyclic antidepressants, vasodilators
- cisapride

If Adalat LA 30/60 mg is administered at the same time as any of these medicinal products, blood pressure should be monitored and, if required, a reduction in the nifedipine dose should be considered.

Nifedipine is contraindicated before the 20th week of pregnancy. Nifedipine should not be used during pregnancy, unless the clinical condition of the woman requires nifedipine treatment. Therefore, nifedipine should be considered only for women with severe hypertension, in whom standard therapy is not effective (see section 4.6).

When nifedipine is used together with intravenously administered magnesium sulphate, blood pressure must be carefully monitored, as an excessive decrease in blood pressure may occur, which may harm both mother and foetus.

For use in specific patient groups, see section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that influence nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, which is present in both the intestinal mucosa and liver. Hence, the concomitant use of medicinal products that induce or inhibit this system can influence the first-pass metabolism (after oral administration) or the excretion of nifedipine (see section 4.4).

Both the degree and duration of interactions should be taken into consideration when Adalat LA 30/60 mg is to be administered together with the medicinal products listed below.

Medicinal products that inhibit the cytochrome P450 3A4 system

When co-administering nifedipine and the active substances listed below, which are known to be weak or moderate inhibitors of this enzyme system, blood pressure should be monitored and, if necessary, the nifedipine dose adjusted (see section 4.2):

Macrolide antibiotics (e.g. erythromycin)
No interaction studies have been performed with nifedipine and macrolide antibiotics. However, since it is known that certain macrolide antibiotics inhibit the CYP3A4 system, an increase in the plasma concentration of nifedipine during concomitant use can not be excluded (see section 4.4).

Azithromycin, although structurally related to macrolide antibiotics, is not an inhibitor of CYP3A4.

Anti-HIV protease inhibitors (e.g. ritonavir)
No clinical interaction studies have been performed with nifedipine and protease inhibitors. Protease inhibitors are known to be inhibitors of the cytochrome P450 3A4 system. Furthermore, medicinal products of this class have been shown to inhibit the cytochrome P450 3A4-mediated metabolism of nifedipine *in vitro*. If these medicines are used together with nifedipine, a substantial increase in the plasma concentration of nifedipine cannot be excluded, due to a decreased first-pass metabolism and decreased elimination (see section 4.4).

Azole-type antifungal agents (e.g. ketoconazole)
No formal interaction studies have been performed with nifedipine and azole-type antifungal agents. Active substances of this class of agents are known to be inhibitors of the cytochrome P450 3A4 system. Therefore, the possibility of an increase in the systemic bioavailability of nifedipine, due to a decreased first-pass metabolism, cannot be excluded during concomitant oral use of both medicines (see section 4.4).

Fluoxetine
No clinical interaction studies have been performed with nifedipine and fluoxetine. Fluoxetine has been shown to inhibit the cytochrome P450 3A4-mediated metabolism of nifedipine *in vitro*. Therefore, the possibility of an increase in nifedipine plasma levels cannot be excluded during concomitant use of both medicines.

Nefazodone
No clinical interaction studies have been performed with nifedipine and nefazodone. Nefazodone is known to be an inhibitor of cytochrome P450 3A4-mediated metabolism. Therefore, the possibility of an increase in nifedipine plasma levels cannot be excluded during concomitant use of both medicines (see section 4.4).

Quinupristin/dalfopristin
Concomitant use of quinupristin/dalfopristin and nifedipine may cause elevated plasma concentrations of nifedipine (see section 4.4).

Valproic acid
No interaction studies have been performed with nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentration of nimodipine, a structurally similar calcium antagonist, by enzyme inhibition, an increase in the plasma concentration and thus an enhanced effect of nifedipine cannot be excluded (see section 4.4).

Cimetidine
Due to inhibition of cytochrome P450 3A4, cimetidine may lead to an increase in the nifedipine plasma level and hence to an increased antihypertensive effect of nifedipine (see section 4.4).

Tricyclic antidepressants, vasodilators
The antihypertensive effect can be potentiated.

Cisapride
Concomitant use of cisapride and nifedipine can lead to elevated plasma levels of nifedipine.

Medicinal products that induce the cytochrome P450 3A4 system

Rifampicin
Rifampicin is a potent cytochrome P450 3A4 inducer. When co-administered with rifampicin, the bioavailability of nifedipine is considerably reduced and thus reduces efficacy. Use of nifedipine in combination with rifampicin is therefore contraindicated (see section 4.3).

Antiepileptics (e.g. phenytoin, carbamazepine, phenobarbital)
Phenytoin induces the cytochrome P450 3A4 system.When phenytoin and nifedipine are co-administered, the bioavailability of nifedipine is reduced and its efficacy is thus attenuated. When both preparations are used concurrently, the clinical response to nifedipine should be observed and, if necessary, an increase in the nifedipine dose should be considered. If the nifedipine dose is increased during concomitant use of both medicines, a reduction in the nifedipine dose should be considered upon cessation of phenytoin therapy.
No formal studies have been performed to investigate possible interactions between nifedipine and carbamazepine or phenobarbital. However, based on experience with nimodipine, a structurally similar calcium antagonist, it cannot be excluded that the concomitant use of carbamazepine or phenobarbital, due to their enzyme-inducing effect, may lead to reduced plasma concentrations and hence to an attenuated effect of nifedipine.

Effects of nifedipine on other medicinal products

Antihypertensive agents
The blood pressure-lowering effect of co-administered antihypertensives can be potentiated by nifedipine, e.g.:
- diuretics
- beta-receptor blockers
- ACE inhibitors
- angiotensin-II (AT1)-receptor antagonists
- other calcium antagonists
- alpha-receptor blockers
- PDE-5 inhibitors
- alpha-methyldopa

Beta-receptor blockers
During concomitant treatment with beta-receptor blockers, onset or exacerbation of heart failure has been observed in individual cases. Patients should therefore be carefully monitored.

Digoxin
Concomitant use of nifedipine and digoxin may lead to reduced digoxin excretion and hence to an increase in the plasma digoxin level. For this reason, the patient should be monitored as a precaution for symptoms of digoxin overdose and plasma levels should be monitored. If necessary. the glycoside dose should be reduced.

Theophyllin
Nifedipine can cause an increase in the plasma theophylline level.

Vincristine
Nifedipine reduces the excretion of vincristine, thereby possibly increasing the undesirable effects of vincristine. A reduction of the vincristine dose should therefore be considered.

Cephalosporins
Upon concomitant administration of cephalosporins (e.g. cefixime) and nifedipine, elevated plasma cephalosporin levels have been observed.

Quinidine
In individual cases, nifedipine causes a decrease in the quinidine plasma level and/or the discontinuation of nifedipine causes a significant increase in the quinidine plasma level. This means that monitoring of the quinidine plasma level and, if required, an adjustment of the quinidine dose is recommended during combined therapy or upon discontinuation of nifedipine. In some cases, there have been reports of a rise in the nifedipine plasma concentration due to quinidine, while in other cases, no change in the pharmacokinetics of nifedipine was observed. If quinidine intake is started during treatment with nifedipine, careful blood pressure monitoring and, if necessary, a reduction in the nifedipine dose is therefore recommended.

Tacrolimus
Tacrolimus is metabolised via the cytochrome P450 3A4 system. Concomitant use of tacrolimus and nifedipine may lead to elevated tacrolimus plasma levels. For this reason, regular monitoring of plasma levels and, if required, a reduction in the tacrolimus dose is recommended.

Interactions with food and drink

Grapefruit juice
Grapefruit juice inhibits the cytochrome P450 3A4 system. Due to reduced first-pass metabolism and delayed excretion, the blood level of nifedipine may be increased and the duration of action prolonged, which may potentiate the antihypertensive effect. After regular consumption of grapefruit juice, this effect may persist for at least 3 days after the last ingestion of grapefruit juice. Consumption of grapefruit or grapefruit juice must therefore be avoided in temporal association with nifedipine treatment (see section 4.2).

Other types of interaction

Spectrophotometric determination of urinary vanillylmandelic acid can lead to falsely elevated values in patients on nifedipine; determination by HPLC remains unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nifedipine is contraindicated before the 20th week of pregnancy. Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be considered only for women with severe hypertension, in whom standard therapy is not effective (see section 4.4).
There is no available experience from suitable and controlled clinical studies with pregnant women.
The information available is not sufficient to exclude negative effects on the fetus and newborn child newborn child.
Experimental studies in animals have shown indications of an embryotoxic, foetotoxic and teratogenic effect of nifedipine (see section 5.3).
From clinical experience, there is no discernible specific prenatal risk, although an increase in cases with perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation, has been reported. It is unclear whether these observations are attributable to the underlying hypertension, its treatment or a specific effect of the active substance.
Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as 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 must not be used during breast-feeding.
Nifedipine is excreted in human milk. The nifedipine concentration in milk is practically comparable with maternal serum concentrations (see section 4.3).

Fertility

In individual cases of *in vitro* fertilisation, calcium antagonists such as nifedipine have been associated with reversible biochemical changes in the head region of spermatozoa, which can lead to impaired sperm function. In cases where repeated *in vitro* fertilisation has failed and no other explanation can be found, calcium antagonists such as nifedipine should be considered as a possible cause.

4.7 Effects on ability to drive and use machines

Treatment with these medicinal products requires regular medical surveillance. As a result of individual variability in response, reaction skills can be altered to such an extent that the ability to drive, use machines or work without a secure foothold is impaired. This applies particularly at the start of treatment, when increasing the dose and switching from another medication and in interaction with alcohol.

4.8 Undesirable effects

Adverse reactions observed in placebo-controlled studies with nifedipine are listed as follows (arranged according to CIOMS III categories; nifedipine n = 2,661; placebo n = 1,486; as at 22 February 2006 and ACTION study: nifedipine n = 3,825; placebo n = 3,840).

The frequency of adverse drug reactions reported with nifedipine is summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness, with frequencies defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Adverse reactions occurring only in post-marketing studies and for which frequency cannot be estimated are listed in the category “not known”.

System organ class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				Leukopenia Anaemia Thrombopenia Thrombocytopenic purpura	Agranulocytosis	
Immune system disorders			Allergic reactions Allergic oedema/angioedema (including laryngeal oedema[1]) Pruritus Exanthem	Urticaria		Anaphylactic/ anaphylactoid reactions
Metabolism and nutrition disorders				Hyperglycaemia		
Psychiatric disorders			Anxiety reactions Sleep disorders			

System organ class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders	Headache	Dizziness Light-headedness Asthenia	Migraine Tremor Par-/dysaesthesia Drowsiness/ fatigue Nervousness			Hypaesthesia
Eye disorders			Visual disturbances			Eye pain
Cardiac disorders		Palpitations	Tachycardia Chest pain (angina pectoris[2])		Myocardial infarction[2]	
Vascular disorders	Oedema (including peripheral oedema)	Vasodilation (e.g. flushing)	Hypotension Syncope			
Respiratory, thoracic and mediastinal disorders			Epistaxis Nasal congestion Dyspnoea			Pulmonary oedema[3]
Gastrointestinal disorders		Constipation Nausea	Gastrointestinal pain and abdominal pain Dyspepsia Flatulence Dry mouth	Gingival hyperplasia Anorexia Bloating Eructation		Bezoars Dysphagia Intestinal obstruction Intestinal ulcers Emesis Oesophagitis
Hepatobiliary disorders			Transient elevation of liver enzyme values	Jaundice		
Skin and subcutaneous tissue disorders		Erythromelalgia, especially at the start of treatment Sweating	Erythema	Allergic photosensitivity Palpable purpura	Exfoliative dermatitis	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			Muscle cramps Swollen joints Myalgia			Arthralgia
Renal and urinary disorders			Polyuria Dysuria In cases of renal insufficiency, transient exacerbation of renal function possible.			
Reproductive system and breast disorders			Erectile dysfunction	Gynaecomastia, which is reversible upon discontinuation of nifedipine.		
General disorders and administration site conditions		General malaise	Nonspecific pain Chills			

[1] = Can lead to a life-threatening outcome

[2] = Uncommonly, especially at the start of treatment, angina pectoris episode may occur, or there may be an increase in the frequency, duration and severity of episodes in patients with existing angina pectoris. In isolated cases, myocardial infarction has been reported to occur.

[3] Cases have been reported when used as tocolytic during pregnancy (see section 4.6).

In dialysis patients with malignant hypertension and hypovolaemia, a considerable decrease 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 to the *Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices), *Abt. Pharmakovigilanz* (Department of Pharmacovigilance), Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: http://www.bfarm.de.

4.9 Overdose

Symptoms of intoxication

The following symptoms are observed in cases of severe intoxication with nifedipine:
Decrease in blood pressure, clouded consciousness including coma, tachyarrhythmias/bradyarrhythmias, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Treatment of intoxication

With regard to treatment, nifedipine elimination and restoration of stable cardiovascular conditions have priority.
After oral ingestion, copious gastric lavage is indicated - possibly in combination with irrigation of the small intestine.
Particularly in cases of intoxication with prolonged-release product, efforts should be made to eliminate nifedipine as completely as possible, including from the small intestine, in order to prevent subsequent absorption of the active substance, which would otherwise be unavoidable.

When administering laxatives, however, inhibition of the intestinal muscles and even intestinal atony should be considered in patients on calcium antagonists.
Nifedipine cannot be dialysed, but plasmapheresis (high plasma protein binding, relatively low volume of distribution) is recommended.
Bradyarrhythmias are treated symptomatically with atropine and/or beta-sympathomimetics; temporary pacemaker therapy is required in the event of critical bradyarrhythmias.
Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 mL of a 10% calcium gluconate solution, given as a slow intravenous injection and repeated if required), As a result, calcium levels may be higher than normal or slightly elevated. If no sufficient increase in blood pressure is achieved with calcium, vasoconstrictive sympathomimetics are additionally administered, such as dopamine (up to 25 µg per kg body weight per minute), dobutamine (up to 15 µg per kg body weight per minute), or noradrenaline, adrenaline or noradrenaline. The dosage of these medications is guided solely by the effect achieved. Additional fluid or volume repletion should be performed with caution and, due to the threat of cardiac overload, together with haemodynamic monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcium antagonist (1,4-dihydropyridine derivative)
Antihypertensive agent
ATC code: C08CA05.

Mechanism of action

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists inhibit the influx of calcium ions through the slow calcium channel in the cell. Nifedipine acts particularly on the smooth

muscle cells of the coronary arteries and on the peripheral resistance vessels. This effect results in vasodilation. At therapeutic doses, nifedipine has practically no direct effect on the myocardium.
In the heart, nifedipine mainly dilates the major coronary arteries by reducing muscle tone, thereby allowing an improvement in perfusion. Peripheral resistance is reduced.
At the start of treatment with the calcium antagonist, there may be a reflex increase in heart rate and cardiac output. However, this increase is not marked enough to compensate for the vasodilation.
During long-term treatment with nifedipine, the initially high cardiac output returns to baseline levels. In patients with hypertension, a particularly marked decrease in blood pressure can be observed after nifedipine.
In a multicentre, randomised, placebo-controlled, double-blind study (ACTION study) with 7,665 patients with stable angina pectoris who were receiving best-practice standard treatment, the effects of nifedipine versus placebo were studied for clinical outcomes. The nifedipine group included 3,825 patients and the placebo group 3,840 patients. The following parameters were used as the primary endpoint for efficacy: combined incidence of death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation. No differences between the two treatment groups were found (P=0.54).
In a predefined analysis of a subset of 3,997 angina pectoris patients with hypertension at study baseline, it was shown that treatment with nifedipine led to a significant reduction (13%) in the primary endpoint for efficacy.
In addition, the safety of nifedipine use was demonstrated in the ACTION study, as the primary endpoint for safety (combined incidence of death from any cause, acute myocardial infarction, debilitating stroke) was the same in both treatment groups (P=0.86).
Nifedipine showed positive effects in 2 out of 3 predefined secondary endpoints. The combined incidence of death, major cardiovascular events, revascularisation and coronary angiography was reduced by 11% (P=0.0012), mainly due to a significant reduction in coronary angiograms. In the nifedipine group, 150 fewer coronary angiograms than in the placebo group were required as the primary examination. The number of total vascular events was reduced by 9% (P=0.027), mainly as a result of fewer invasive percutaneous coronary interventions and fewer bypass surgeries. In total, 89 fewer primary procedures were needed in the nifedipine group than with placebo. For the third of the secondary endpoints, i.e. major cardiovascular events, there were no observable differences between the two treatment groups (P=0.26).

Paediatric population

Limited information is available on nifedipine in its various pharmaceutical forms and dosages, both for acute and chronic hypertension, compared with other antihypertensives. Antihypertensive effects of nifedipine have been demonstrated, but dosage recommendations and long-term data on safety and effects on the cardiovascular system have not been investigated. There are no paediatric pharmaceutical forms.

5.2 Pharmacokinetic properties

Adalat LA 30/60 mg is a pharmaceutical form based on the osmotic pump principle. The two-layer tablet contains the active substance nifedipine in one layer, as well as other components which, together with water or gastrointestinal fluid, produce an aqueous suspension. The second layer contains polymers, which expand in liquid and thus exert pressure on the first layer. The tablet is surrounded by a water-permeable membrane, in which an aperture has been created, through which the active substance can escape. Nifedipine is continuously absorbed throughout the entire gastrointestinal tract over a 24-hour period. Absorption post-ingestion is virtually constant within the range of 6-18 hours. As a consequence, steady state is reached as early as after the second administration and minimal plasma level fluctuations occur over the course of the day.
The polymers are not absorbed and, after release of the active substance, the tablet shell is excreted unchanged with the faeces.

Nifedipine is 95-98% bound to plasma protein (albumin). For nifedipine, a mean volume of distribution V_{ss} of 0.77-1.12 L/kg was found.

Nifedipine is almost completely metabolised (high first-pass effect) in the liver, mainly via oxidative processes. These metabolites show no pharmacodynamic activities. Neither the unchanged substance nor the metabolite M-1 is renally eliminated to any significant degree (<0.1% of the dose). The polar metabolites M-2 and M-3 are found at a rate of approximately 50% of the dose in the urine (partially in conjugated form), with the major fraction being excreted within 24 hours. The remainder is excreted with the faeces.

In a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and Cmax of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (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 section 4.4).

Bioavailability

The pharmacokinetics of Adalat LA 30/60 mg is characterised by low peak plasma levels and low peak-trough fluctuation. The 24-hour plasma profiles show a plateau at steady state, thus allowing once-daily administration.
Relative bioavailability compared with the Adalat capsule is 75%.
The following table shows peak plasma concentrations (C_{max}), times to peak plasma concentrations (T_{max}) and the area under the concentration-time curve (AUC) of nifedipine, after single and multiple doses of Adalat LA 30/60 mg (geometric means):

Formulation		C_{max} [µg/L]	AUC [µg x h/L]	t_{max}** [h]
Adalat LA 30 mg	after single dosing	16-22	290-480	11-17
	after repeated dosing	31	514	9
Adalat LA 60 mg	after single dosing	30-36	520-820	10-17
	after repeated dosing	49-62	720-980	7-12

** arithmetic means

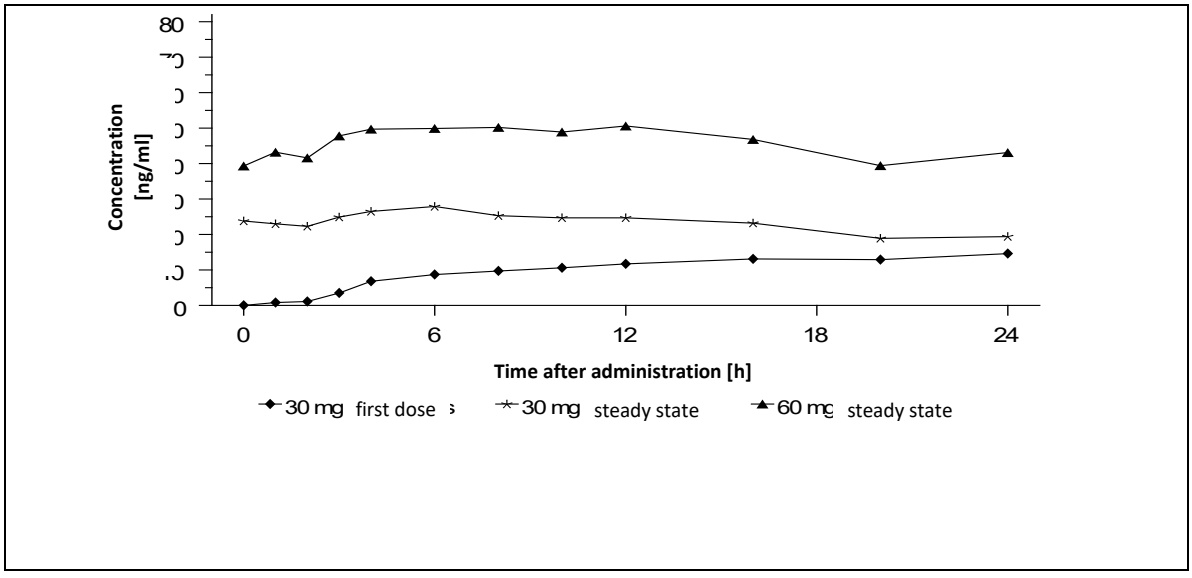

Fig.: Plasma nifedipine concentrations after single dosing with Adalat LA 30 mg and after repeated dosing with Adalat LA 30 mg and 60 mg (geometric means)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute toxicity, chronic toxicity, mutagenic potential and tumorigenic potential.

a) Acute toxicity
Acute toxicity was investigated in various animal species. No specific sensitivity was shown.

b) Chronic toxicity
Studies on rats and dogs showed no specific toxic effect of nifedipine.

c) Mutagenic and tumorigenic potential
As the *in vivo* and *in vitro* studies were negative without exception, a mutagenic effect in humans can be sufficiently excluded.
A long-term study (2 years) on rats produced no indications of tumorigenic effects for nifedipine.

d) Toxicity to reproduction
Experimental studies have produced indications of teratogenic effects in three animal species (rat, rabbit, mouse), including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformations of the ribs. The digital anomalies and malformations of the extremities are possibly attributable to impaired uterine perfusion, but have also occurred in animals receiving nifedipine only after organogenesis.
No experience is available with use in humans during the first six months of pregnancy. Nifedipine use without adverse sequelae in the last three months of pregnancy has been described for a small number of cases. Nifedipine has a tocolytic effect.
Nifedipine passes into breast milk. No sufficient experience is available for use during breast-feeding.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose acetate, red iron oxide (E172), hyprolose, hypromellose, macrogol 3350, macrogol 200,000, macrogol 5 million, magnesium stearate, sodium chloride, propylene glycol, titanium (IV) oxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene (colourless) / aluminium foil - or polyamide/aluminium/polyvinylchloride / aluminium foil - blisters in folding boxes

Adalat LA 30 mg
Packs with 30 prolonged-release tablets, each with 30 mg nifedipine
Packs with 50 prolonged-release tablets, each with 30 mg nifedipine
Packs with 100 prolonged-release tablets, each with 30 mg nifedipine
Hospital packs with 100 prolonged-release tablets, each with 30 mg nifedipine

Adalat LA 60 mg
Packs with 30 prolonged-release tablets, each with 60 mg nifedipine
Packs with 50 prolonged-release tablets, each with 60 mg nifedipine
Packs with 100 prolonged-release tablets, each with 60 mg nifedipine
Hospital packs with 100 prolonged-release tablets, each with 60 mg nifedipine

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
D-13342 Berlin
Tel.: (0214) 30 - 5 13 48
Fax: (0214) 30 - 5 16 03
e-mail address: medical-information@bayer.com

8. MARKETING AUTHORISATION NUMBERS

Adalat LA 30 mg	MA No.: 37545.00.00
Adalat LA 60 mg	MA No.: 37545.01.00

9. DATE OF FIRST AUTHORISATIONS/RENEWAL OF THE AUTHORISATIONS

Adalat LA 30 mg
Date of first authorisation: 20 April 1998
Date of latest renewal: 10 November 2006

Adalat LA 60 mg
Date of first authorisation: 20 April 1998
Date of latest renewal: 10 November 2006

10. DATE OF REVISION OF THE TEXT

July 2016

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription