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NAME OF THE MEDICINAL PRODUCT

Adalat LA 30 mg prolonged-release tablets

Adalat LA 60 mg prolonged-release tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Adalat LA 30 mg prolonged-release tablets

Each prolonged-release tablet contains 30 mg nifedipine

Adalat LA 60 mg prolonged-release tablets

Each prolonged-release tablet contains 60 mg nifedipine

PHARMACEUTICAL FORM

Adalat LA 30 mg prolonged-release tablets

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

Adalat LA 60 mg prolonged-release tablet

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

CLINICAL PARTICULARS

Indication(s)

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

Treatment of 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years in a multi-national, randomised, double-blind, prospective study. Nifedipine (Adalat LA) was shown to reduce cardiovascular and cerebrovascular events to a comparable degree as a standard diuretic combination.

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Dosage and method of administration

Method of administration

Oral use

Dosage regimen

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

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

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

- For **coronary heart disease**

Chronic stable angina pectoris (angina of effort)

1 Adalat LA 30 mg tablet once daily (1 x 30 mg/day)

1 Adalat LA 60 mg tablet once daily (1 x 60 mg/day)

- For **hypertension**

1 Adalat LA 30 mg tablet once daily (1 x 30 mg/day)

1 Adalat LA 60 mg tablet once daily (1 x 60 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.

Depending on the severity of the disease and the patient's response the dose can be inLAeased in stages up to 120 mg once daily.

Coadministration 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.

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Administration

The tablets must not be chewed or broken up!

As a rule Adalat LA 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*")

Additional information on special populations

Pediatric patients

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

Geriatric 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 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 "*Special warnings and precautions for use*")

Patients with renal impairment

Based on pharmacokinetic data no dosage adjustment is required in patients with renal impairment

Contraindications

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

Nifedipine is contraindicated in pregnancy before week 20 and during breastfeeding (see "*Fertility, pregnancy and lactation*").

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

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

Nifedipine must not be used in combination with rifampicin because no efficient plasma levels of nifedipine may be obtained due to enzyme induction (see "*Interaction with other medicinal products and other forms of interactions*").

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 mm Hg), 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 when administered during and after the period of organogenesis.

From the clinical evidence available a specific prenatal risk has not been identified. Although an inLAease in perinatal asphyxia, caesarean delivery 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 administered nifedipine with i.v. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and fetus.

As with other non-deformable material (see "*Instructions for use / handling*") care should be used when administering Adalat LA 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 desLAibed without known history of gastrointestinal disorders.

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

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 "*Dosage and method of administration"* Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see "*Interaction with other medicinal products and other forms of interaction*").

Drugs, which are inhibitors of the cytochrom P450 3A4 system and therefore may lead to inLAeased plasma concentrations of nifedipine are, e.g.:

- maLAolide 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 "*Dosage and method of administration*".

Interaction with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see "*Special warnings and precautions for use*").

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin

Rifampicin strongly induces the cytochrome P450 3A4 system. Upon coadministration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contra-indicated (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 nifedipine dose considered (see "*Dosage and method of administration*").

MaLAolide antibiotics (e.g., erythromycin)

No interaction studies have been carried out between nifedipine and maLAolide antibiotics. Certain maLAolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an inLAease of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see "*Special warnings and precautions for use*").

Azithromycin, although structurally related to the class of maLAolide antibiotics is void of CYP3A4 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 per¬formed. 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 inLAease in plasma concentrations of nifedipine due to a deLAeased first pass metabolism and a deLAeased 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 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 inLAease in systemic bioavailability of nifedipine due to a deLAeased first pass metabolism cannot be excluded (see "*Special warnings and precautions for use*").

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 inLAease of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see "*Special warnings and precautions for use*").

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 inLAease of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see "*Special warnings and precautions for use*").

Quinupristin / Dalfopristin

Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to inLAeased plasma concentrations of nifedipine (see "*Special warnings and precautions for use"*).

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 inLAease the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an inLAease in nifedipine plasma concentrations and hence an inLAease in efficacy cannot be excluded (see "*Special warnings and precautions for use*").

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plas¬ma 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 inLAeased plasma concentrations of nifedipine.

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

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an inLAease of the nifedipine dose considered. If the dose of nifedipine is inLAeased 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 phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a deLAease in nifedipine plasma concentrations and hence a deLAease in efficacy cannot be excluded.

Effects of nifedipine on other drugs

Blood pressure lowering drugs

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

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

When nifedipine is administered simultaneously with ß-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 inLAease in plasma concentrations of digoxin. 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 or, after discontinuation of nifedipine, a distinct inLAease 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 inLAeased plasma concentrations of nifedipine upon coadministration 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 deLAeased.

Tacrolimus

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

Drug-food interactions

Grapefruit juice

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 deLAeased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect may be inLAeased. 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 is therefore to be avoided while taking nifedipine (see "*Dosage and method of administration*").

Other forms of interaction

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

Fertility, pregnancy and lactation

Pregnancy

Nifedipine is contraindicated in pregnancy before week 20 (see ”*Contraindications*”).

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

<The following comprehensive mandatory statement (a) on reproduction toxicity is to be treated as an alternative to the more detailed optional statement (b) on reproduction toxicity below.>

a) In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity .

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.

Fertility

In-vitro fertilization

In single cases of in vitro fertilization 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 fertilization, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Effects on ability to drive or use machines

Reactions to the drug, 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

Tabulated list of adverse reactions

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

deLAeasing 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 Vasodilatation	Hypotension Syncope		

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System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Respiratory, thoracic, and mediastinal disorders		Nosebleed Nasal congestion		Dyspnea
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 inLAease in liver enzymes		Jaundice
Skin and subcutaneous tissue disorders		Erythema		Toxic Epidermal NeLAolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal and connective tissue disorders		Muscle LAamps 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		

[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.

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).

Bradycardiac heart rhythm disturbances may be treated symptomatically with ß-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 - 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 inLAease in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage of these drugs is determined solely by the effect obtained.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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. 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 inLAeased poststenotic blood flow and an inLAeased 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 inLAeased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex inLAease in heart rate and thus in the cardiac output. However, this inLAease is not enough to compensate for the vasodilation. In addition nifedipine inLAeases sodium and water exLAetion both in the short-term and long-term use. The blood-pressure-lowering effect of nifedipine is particularly pronounced in hypertensive patients.

In a 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, nifedipine (Adalat LA) was shown to reduce cardiovascular and cerebrovascular events to a comparable degree as a standard diuretic combination

In the multicenter, 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 Adalat 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 Adalat 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 Adalat LA led to a significant 13% reduction of the primary endpoint for efficacy.

Adalat 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).

AdalatLA 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).

Pharmacokinetic properties

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 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 (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 nifedipine 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 LA 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 (0.9-1.2 ng/ml).

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.

Metabolism / Biotransformation

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

Nifedipine is exLAeted in the form of its metabolites predominantly via the kidneys, and about 5 - 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1 %) in the urine.

Elimination / Excretion

The terminal elimination half-life is 1.7 to 3.4 h in conventional formulations (nifedipine capsules). The terminal half-life after Adalat LA 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 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 inLAeased 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 "*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.

Reproduction toxicity

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 / deLAeased 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

Cellulose acetate,

Hydroxypropyl cellulose,

Hypromellose,

Iron oxide red (E172/C.I.77491),

Magnesium stearate,

Polyethylene glycol 3350,

Polyethylene oxide,

Propylene glycol,

Sodium chloride,

Titanium dioxide (E171/C.I.77891).

Incompatibilities

None

Special precautions for storage

Do not store above 30°C

Keep out of reach of children

Instructions for use / handling

In Adalat LA the medication is contained within a non-absorbable shell that slowly releases the drug 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 LA 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.

Nature and contents of container

Adalat LA 30 mg / 60 mg tablets:

Alu/Alu-blister : 3 x 10 Tablets

Only on prescription

MANUFACTURED BY

Bayer Pharma AG

51368 Leverkusen, Germany

A Division of Bayer East Africa Ltd

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