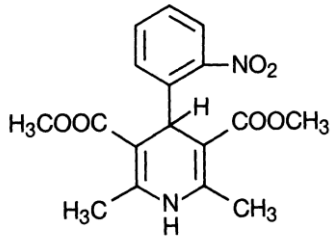
ADALAT® 10 AND ADALAT® 20 TABLETS

PRODUCT INFORMATION

NAME OF THE MEDICINE

Nifedipine is dimethyl-1,4-dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-3,5-pyridine dicarboxylate, $C_{17}H_{18}N_2O_6$, MW 346.3, CAS Registry No. [21829-25-4]. Its structural formula is shown below.



Nifedipine is a yellow crystalline substance practically insoluble in water, and sparingly soluble in absolute ethanol. It is sensitive to light.

DESCRIPTION

Adalat tablets are round, pink-grey, film-coated tablets containing micronised nifedipine 10 mg or 20 mg. Adalat tablets also contain the following inactive ingredients: microcrystalline cellulose, maize starch, polysorbate 80, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide, iron oxide red (CI 77491), and lactose.

PHARMACOLOGY

Adalat (nifedipine) 10 or 20 is a calcium ion influx inhibitor (calcium channel blocker or calcium antagonist).

Pharmacokinetics

After oral administration, the absorption of nifedipine from the tablet is delayed (t_{max} 1.5 to 4.2 hours) compared to a liquid capsule formulation (t_{max} 0.5 to 2.17 hours). The bioavailability of the tablet is 45 – 56%.

Nifedipine is about 95% bound to plasma protein (albumin). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

Nifedipine is almost completely metabolised in the body with only traces detected in the urine in an unchanged form. 70-80% of the dose is excreted via the kidneys in the form of highly water-soluble pharmacologically inactive metabolites. The remainder is excreted in the faeces, also in a metabolised form. The half-life of an immediate release dose form shows a mean of approximately 1.7 - 3.4 hours. Administration of the tablet results in a half-life of about 6 - 12 hours. (Continuing absorption of residual nifedipine from the gastrointestinal tract probably contributes to the prolonged half-life observed).

The pharmacological action of nifedipine persists for up to twelve hours after administration of the tablet.

In cases of impaired liver function, the elimination half-life is distinctly prolonged and the total clearance is reduced. A dose reduction may be necessary in severe cases.

Pharmacological actions

Cardioprotective Coronary Treatment

The contractile processes of vascular smooth muscle and cardiac muscle are dependent upon calcium ions. Calcium ions enter these cells during depolarisation as slow ionic transmembrane currents. Nifedipine specifically inhibits slow inward calcium ion channels without changing serum calcium concentrations. In so doing, two distinct beneficial effects are produced which reduce anginal pain in individuals with ischaemic heart disease.

Nifedipine Improves Myocardial Oxygen Supply

Nifedipine is a potent relaxant of arterial smooth muscle. It dilates main coronary arteries and arterioles both in normal and in ischaemic myocardial regions without inducing a steal phenomenon. Nifedipine is also a potent inhibitor of coronary artery spasm. These effects increase myocardial oxygen delivery at rest and during exercise in patients with chronic stable angina, and in patients with episodes of coronary artery spasm.

Nifedipine Reduces Myocardial Work Through Afterload Reduction

As with myocardial cell contraction, regulation of the contraction of vascular smooth muscle is also dependent upon intracellular calcium ion concentration. By reducing the influx of calcium ions into vascular smooth muscle, nifedipine causes relaxation and peripheral vasodilatation. Peripheral vasodilatation reduces the impedance (afterload) against which the heart works. This unloading of the heart indirectly reduces myocardial energy consumption and oxygen requirements. Ventricular emptying is also facilitated by the reduction in impedance.

A third possible effect seen experimentally is:

Nifedipine Directly Decreases Myocardial Oxygen Consumption

During myocardial fibre depolarisation, elevation of intracellular calcium ion concentration triggers the contractile process and increases the amount of adenosine-5'-triphosphate (ATP) hydrolysed.

By inhibiting the transmembrane flux of calcium that enters myocardial cells, and hence decreasing intracellular calcium concentration, nifedipine reduces the amount of ATP hydrolysed and thereby decreases the amount of oxygen consumed by the heart. The clinical significance of this effect is as yet undecided. Unlike beta-blockers, nifedipine does not abolish responsiveness of the heart to beta-adrenergic stimulation.

Antihypertensive Effect

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 reflux increase in heart rate and thus in the cardiac output. However this increase is not enough to compensate for the vasodilation.

INDICATIONS

Adalat 10 and 20 are indicated for:

i. the management of chronic stable angina pectoris and vasospastic angina pectoris (Prinzmetal's angina, variant angina) due to coronary heart disease.

ii. the treatment of hypertension.

CONTRAINDICATIONS

Known hypersensitivity to nifedipine or any of the excipients.

Pregnancy and during lactation.

Cardiovascular shock.

Within the first 8 days after an acute episode of myocardial infarction.

Concomitant administration with rifampicin (see INTERACTION WITH OTHER MEDICINES).

PRECAUTIONS

Excessive Hypotension

Adalat may be used in combination with beta-blocking medicines and other antihypertensive agents, but the possibility of potentiation of existing antihypertensive therapy should be noted. Care must also 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.

Increased Angina

As with other vasoactive substances, angina pectoris attacks may very rarely occur at the start of the treatment with nifedipine. The occurrence of myocardial infarction has been described in isolated cases, although it was not possible to distinguish this from the natural course of the underlying disease.

Beta-Blocker Withdrawal

When nifedipine is administered simultaneously with beta-blockers the patient should be carefully monitored, since deterioration of heart failure may develop in isolated cases.

Nifedipine has no inherent anti-arrhythmic action and therefore gives no protection against any arrhythmias which may result from abrupt withdrawal of beta-blockers. Any such withdrawal of beta-blockers should be gradual over a period of several days.

Congestive Heart Failure

The onset of cardiac insufficiency has occasionally been observed during clinical use. Care should be observed with patients whose cardiac reserve is poor, or who are receiving large doses of beta-blockers.

Outflow Obstruction

Adalat should be used with caution in the presence of fixed left ventricular outflow obstruction.

Peripheral Oedema

Mild to moderate peripheral oedema typically associated with arterial vasodilatation and not due to left ventricular dysfunction, occurs in one in ten patients treated with nifedipine. This oedema occurs primarily in the lower extremities and usually responds to diuretic therapy.

Other

Adalat contains lactose, patients with a rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Adalat.

Other Nifedipine Formulations

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

Effects on fertility

In single cases of *in vitro* fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Use in Pregnancy (Category C)

Nifedipine carries the potential for fetal hypoxia, caesarean deliveries, prematurity and intrauterine growth retardation, which may be associated with maternal hypotension. Accordingly, it is contraindicated throughout pregnancy.

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 are possibly a result of compromised uterine blood flow. 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 and several times the recommended maximum dose for humans. There are no adequate and well controlled studies in pregnant women.

Use in Lactation

Nifedipine passes into breast milk. Insufficient evidence is available to determine whether effects of nifedipine occur in infants. Breast-feeding should first be stopped if nifedipine treatment becomes necessary during the breast-feeding period.

Paediatric use

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

Use in Patients with Impaired Liver Function

Adalat 10 and 20 should be used with caution in patients with mild, moderate or severe impaired liver function (see PHARMACOLOGY). A dose reduction may be required (see DOSAGE AND ADMINISTRATION). Close monitoring of response and metabolic effect should apply. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment. Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Use in the Elderly

The pharmacokinetics of Adalat are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Use in Diabetes

A possible interference with glucose-induced insulin release should be taken into account when treating diabetic patients with nifedipine but based on extensive experience it is probably more accurate to conclude that nifedipine has no true diabetogenic potential.

Carcinogenicity/Mutagenicity

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. *In vitro* and *in vivo* mutagenicity studies were negative.

INTERACTION WITH OTHER MEDICINES

Nifedipine is metabolised via cytochrome P450 3A4 (CYP3A4), located in the intestinal mucosa and the liver. Medicines that are known to inhibit or induce CYP3A4 may therefore alter the first pass or the clearance of nifedipine.

Drugs, which are inhibitors of CYP3A4 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 drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Drugs that affect nifedipine

Nifedipine is metabolised via CYP3A4, located in the intestinal mucosa and the liver. Medicines that are known to inhibit or induce CYP3A4 may therefore alter the first pass or the clearance of nifedipine.

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 CYP3A4. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated.

Upon co-administration of the following weak to moderate inhibitors of CYP3A4, blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see DOSAGE AND ADMINISTRATION).

Macrolide antibiotics (e.g. erythromycin)

No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit CYP3A4 mediated metabolism of other medicines, and could increase plasma concentrations of nifedipine if administered concomitantly.

Azithromycin, although structurally related to the class of macrolide antibiotics does not inhibit CYP3A4.

Anti-HIV Protease Inhibitors

A clinical study investigating the potential interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Medicines of this class are known to inhibit the CYP3A4. In addition, drugs of this class have been shown to inhibit *in vitro* the CYP3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first-pass metabolism and decreased elimination cannot be excluded.

Azole anti-mycotics (e.g. ketoconazole)

A formal interaction study investigating the potential of a drug interaction between nifedipine and these medicines has not yet been performed. These medicines are known to inhibit CYP3A4. When administered orally with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded.

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 CYP3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded (see PRECAUTIONS).

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 CYP3A4 mediated metabolism of other medicines. Therefore an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded.

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine, with the effect varying markedly between individuals.

Valproic acid

No formal studies have been performed to investigate the interaction of nifedipine with valproic acid, but it has been shown to increase the plasma concentrations of another dihydropyridine calcium channel blocker (nimodipine) through enzyme inhibition. Therefore an increase in the plasma concentrations of nifedipine is possible which may mean that an adjustment in the dosage of nifedipine may be required.

Cimetidine

Elevation of plasma nifedipine levels during cimetidine administration has been reported. It is suggested that patients taking both nifedipine and cimetidine should be carefully monitored. In case of hypotension, the dosage of nifedipine should be reduced or the patient should be treated with ranitidine, as the interaction with this medicine and nifedipine is less pronounced.

Diltiazem

Diltiazem decreases the clearance of nifedipine and, hence, increases plasma nifedipine levels. Therefore caution should be exercised when the two medicines are used concomitantly and a reduction in the dose of nifedipine may be necessary.

Further studies

Cisapride

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

CYP3A4-inducing anti-epileptic drugs such as phenytoin, carbamazepine and phenobarbitone

Phenytoin induces CYP3A4. Co-administration of phenytoin with nifedipine reduces the bioavailability of nifedipine. When both medicines are concomitantly administered, the clinical response to nifedipine should be monitored and an increase in the nifedipine dose considered, if necessary. If the dose of nifedipine is increased during co-administration of both medicines, a reduction of the nifedipine dose should be considered when phenytoin is discontinued. No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazeipine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker, nimodipine, through enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy cannot be excluded.

Effects of nifedipine on other drugs

Blood pressure lowering drugs

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

- *diuretics*

- *β-blockers*
- *ACE-inhibitors*
- *angiotensin I (ATI) receptor – antagonists*
- *other calcium antagonists*
- *α-adrenergic blocking agents*
- *PDE5 inhibitors*
- *α-methyldopa*

When nifedipine is administered simultaneously with β-receptor blockers, the patient should be carefully monitored, since fairly severe hypotension can occur; deterioration of heart failure is also known to develop in isolated cases.

Digoxin

The simultaneous administration of nifedipine and digoxin can lead to reduced digoxin clearance and hence an increase in the plasma digoxin level. The patient should therefore be checked for symptoms of digoxin overdose as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma digoxin concentration.

Quinidine

When nifedipine and quinidine have been administered simultaneously, lowered quinidine levels or, after discontinuation of nifedipine, a distinct increase in the plasma quinidine level have been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine concentration and, if necessary, adjustment of the dose are recommended. Some authors reported increased plasma levels of nifedipine upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of nifedipine. Therefore, if quinidine is added to existing nifedipine therapy, blood pressure should be monitored, and if necessary the dose of nifedipine should be reduced.

Tacrolimus

Tacrolimus is metabolised by CYP3A4. Published data indicate that the dose of nifedipine administered simultaneously with tacrolimus may be reduced in individual cases. Upon co-administration of both medicines, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose should be considered.

Drug-food interactions

Grapefruit

Concomitant intake of grapefruit juice inhibits the oxidative metabolism of nifedipine resulting in increased plasma concentration which may cause an increased blood pressure lowering effect. 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.

Interactions shown not to exist

In drug interaction studies, aspirin, omeprazole, pantoprazole, ranitidine, and cerivastatin did not have clinically significant effects on the pharmacokinetics of nifedipine. Nifedipine

did not have clinically significant effects on the pharmacokinetics of cerivastatin, or on the effect of 100 mg aspirin on platelet aggregation and bleeding time.

Candesartan cilexetil, Irbesartan, Doxazosin

The blood pressure lowering effect of these agents may be potentiated by co-administration with nifedipine, so caution should be used in initiating combination therapy. Concomitant administration of irbesartan or doxazosin and nifedipine has no effect on the pharmacokinetics of nifedipine, and concomitant administration of candesartan cilexetil and nifedipine has no effect on the pharmacokinetics of either medicine.

Others

Case reports of increased plasma theophylline concentrations due to nifedipine administration have been reported. Nifedipine has also been reported to have a potentiating effect on terbutaline and salbutamol induced bronchodilation in asthmatics.

Other forms of interactions

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

Effect on Ability to Drive and Use Machines

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

Effect on Laboratory Tests

Rare, usually transient, but occasionally significant elevations of enzymes such as AP, CPK, LDH, AST (SGOT) and ALT (SGPT) have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Nifedipine like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in nifedipine treated patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

ADVERSE EFFECTS

Adverse Drug Reactions (ADRs) listed under “common” were observed with a frequency below 3 % with the exception of oedema (9.9 %) and headache (3.9 %). ADR is defined as a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial database: nifedipine n = 6,486; placebo n = 5,326) are listed below. The frequencies are defined as:

Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10000 to < 1/1000

Table 1. ADRs reported based on clinical trial data

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders			Purpura
Immune system disorders		Allergic reaction Allergic Oedema/angioedema (incl. larynx oedema*)	Urticaria
Psychiatric disorders		Anxiety reactions Sleep disorders	
Nervous system disorders	Headache Dizziness	Paraesthesia Somnolence Tremor Vertigo Migraine	Hypaesthesia Dysaesthesia
Eye disorders		Visual disturbances	
Cardiac disorders	Palpitation	Chest pain Angina pectoris Tachycardia	
Vascular disorders	Oedema Vasodilataion	Syncope Hypotension	
Respiratory, thoracic, and mediastinal disorders		Dyspnoea Nosebleed Nasal congestion	
Gastrointestinal disorders	Nausea Constipation	Gastrointestinal and abdominal pain Dry mouth Dyspepsia	Gingival hyperplasia Gastrointestinal disorder

System Organ Class	Common	Uncommon	Rare
		Vomiting Flatulence Diarrhoea	GGTP increased
Hepatobiliary disorders		Increase in transaminases	
Skin and subcutaneous tissue disorders		Pruritis Rash Sweating Erythema Skin disorder	
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle cramps Joint swelling	
Renal and urinary disorders		Nocturia Polyuria Dysuria	Urinary frequency increased
General disorders and administration site conditions	Feeling unwell Asthenia	Unspecific pain Chills	Abdomen enlarged Photosensitivity reaction
Reproductive system and breast disorders		Erectile dysfunction	

* = may result in life-threatening outcome

Serious or Life Threatening Reactions:

Anaphylactic reactions have occurred with other formulations of nifedipine.

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

The medicine has, like other members of its class, negative inotropic effects on isolated myocardial tissue. Such effects have not been seen in studies in intact animals or in man. Nevertheless, it may theoretically precipitate cardiac failure. Aggravation of cardiac insufficiency has occasionally been reported in patients with compromised cardiac function or when nifedipine is given in combination with beta-blockers.

Acute pulmonary oedema precipitated by nifedipine in a patient with fixed outflow obstruction has been reported. Care should therefore be taken with patients whose cardiac reserve is poor.

Post-marketing Experience

A small number of events identified during ongoing post-marketing surveillance associated with nifedipine for which a frequency could not be estimated are listed in the table below.

Table 2. ADRs reported based on post-marketing experience

System Organ Class (MedDRA)	Not known
Blood and lymphatic system disorders	Agranulocytosis Leukopenia
Immune system disorders	Anaphylactic/ anaphylactoid reactions
Metabolism and nutrition disorders	Hyperglycaemia
Nervous system disorders	Hypoaesthesia Somnolence
Eye disorders	Eye pain
Cardiac disorders	Chest pain (Angina pectoris)
Respiratory, thoracic, and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Vomiting Gastro-oesophageal sphincter insufficiency Gum hyperplasia
Hepatobiliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Toxic Epidermal Necrolysis (exfoliative dermatitis) Erythromelalgia Photosensitivity allergic reaction Palpable purpura Gynaecomastia
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia

DOSAGE AND ADMINISTRATION

Dosage should be individualised depending on severity of disease, patient's tolerance and responsiveness to Adalat (nifedipine) 10 or 20 and to concurrent antihypertensive medications (see Interaction with Other Medicines).

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

The recommended initial dose is 10-20 mg twice daily swallowed with a little fluid, with or without food. The tablets must not be chewed or broken up. Grapefruit juice is to be avoided. The usual adult dose is 20 mg twice daily. If required, the dose may be increased up to 40 mg twice daily. The maximum daily dose of 80 mg should not be exceeded. The recommended dose interval is about 12 hours.

Due to its pronounced anti-ischaemic and antihypertensive action, Adalat should be discontinued gradually, particularly when high doses are used.

Adalat 10 tablets permit dosage titration. Dose titration is particularly recommended for patients with severe cerebrovascular disease or patients of low body weight, on multiple therapies with other antihypertensive medicines, or for whom adverse reactions would occur at the higher initial dose. These patients are likely to have an excessive reaction to nifedipine. In addition, a finer dose adjustment is desirable in patients who experience side effects in response to the nifedipine treatment and should be individually stabilised with Adalat 10 tablets. Patients with hepatic dysfunction should commence therapy at 10 mg twice daily with careful monitoring.

Co-administration with CYP3A4 inhibitors or inducers may require nifedipine dose adjustment or for nifedipine not to be used at all (see Interaction with Other Medicines).

OVERDOSAGE

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 (Adalat 10 and Adalat 20), 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 may be advisable.

Hypotension, as a result of cardiogenic shock and arterial vasodilatation, can be treated with calcium (10-20 mL of a 10% calcium gluconate solution administered slowly intravenously and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If the effects are inadequate, the treatment can be continued with ECG monitoring and additional β-sympathomimetics if necessary (e.g., isoprenaline 0.2 mg slowly intravenously as a continuous infusion of 5 µg/min). If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, 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.

Contact Poisons Information Centre 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Adalat 10: Pink-grey biconvex lacquered tablets, one side marked A10, each containing 10 mg nifedipine. Red blister strips of 10 tablets in boxes containing 20 or 60 tablets.

Adalat 20: Pink-grey biconvex lacquered tablets, one side marked 1U, the reverse side with the Bayer cross, each containing 20 mg nifedipine. Red blister strips of 10 tablets in boxes containing 20 or 60 tablets.

Not all pack sizes may be marketed.

Nifedipine is highly light sensitive. The tablets should be protected from light and should be stored in the manufacturer's original container. Tablets must only be removed from the packaging immediately before use. Broken tablets should not be used. Tablets should be stored below 25°C. Avoid freezing.

Container types for Adalat 10 mg and Adalat 20 mg tablet:

Blister Pack (PVC/Al)

Blister Pack (PVC/PVDC/Al)

Blister Pack (PP/Al)

Not all packaging material types may be marketed.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD
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875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG: 5 March 1993

DATE OF MOST RECENT AMENDMENT: 3 May 2016

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