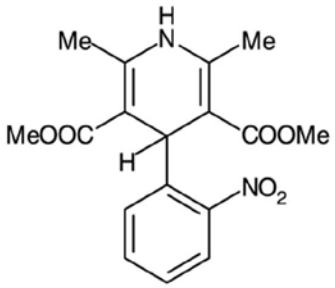
PRODUCT INFORMATION

ADDOS XR

NAME OF THE MEDICINE

Nifedipine. The chemical name for nifedipine is dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. Its structural formulais:



$C_{17}H_{18}N_2O_6$ Molecular weight: 346.3 Cas No.: 21829-25-4

DESCRIPTION

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

Addos XR tablets come in two strengths and contain either 30 mg or 60 mg of nifedipine. The tablets also contain the following excipients: purified talc, povidone, lactose monohydrate, carbomer 934P, hypromellose, colloidal anhydrous silica, magnesium stearate, titanium dioxide, iron oxide red CI77491, macrogol 4000 and Eudragit E100. The tablets are gluten free.

PHARMACOLOGY

Nifedipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the muscle cells through specific ion channels. Nifedipine selectively inhibits the transmembrane influx of calcium through the slow channel without affecting the transmembrane influx of sodium through the fast channel to any significant degree. This results in a reduction of free calcium ions available within the muscle cells and an inhibition of the contractile process. Nifedipine does not affect total serum calcium. The specific mechanisms by which nifedipine relieves angina and reduces blood pressure have not been fully determined but are believed to be brought about largely by its vasodilatory action.

Hypertension. The mechanisms by which nifedipine reduces arterial blood pressure involve peripheral arterial vasodilatation and the resulting reduction in peripheral vascular resistance. The increased peripheral resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in free calcium in the cytosol.

The binding of nifedipine to voltage dependent and possibly receptor operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. The reduction in calcium influx by nifedipine causes arterial vasodilatation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

Angina. The precise mechanism by which inhibition of calcium influx relieves angina has not been fully determined. Some of the possible mechanisms include vasodilatation and reduction of oxygen utilisation.

Nifedipine dilates the main coronary arteries and coronary arterioles in both normal and ischaemic regions, resulting in an increase in blood flow and hence in myocardial oxygen delivery in patients with coronary artery spasm.

Nifedipine reduces arterial blood pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral vascular resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

Angina clinical trials. The pivotal clinical studies were performed in patients with chronic stable angina. In these studies, nifedipine extended release tablets at doses of 30 and 60 mg once daily improved exercise tolerance test (ETT) parameters in reference to baseline. Nifedipine extended release tablets, 30 mg daily showed a small but suboptimal benefit. When titrated to the dose of 60 mg once daily, the tablets were as effective as atenolol 100 mg once daily. In patients already receiving beta-blocker therapy, nifedipine extended release tablets improved ETT parameters and time to 1 mm ST depression, and at doses of up to 90 mg once daily was more effective than modified release nitrates (isosorbide mononitrate 50 mg once daily or isosorbide dinitrate 20 to 40 mg twice daily). However in this particular study, ETT performance was measured at 22 to 24 hours after the last dose of nifedipine extended release tablets and isosorbide mononitrate, and about 15 hours after the last dose of isosorbide dinitrate. Therefore the higher efficacy observed for nifedipine extended release tablets may be attributable to the difference in pharmacokinetics to nitrates. In pivotal and supportive clinical studies, the duration of treatment with nifedipine extended release tablets was limited to two to twelve weeks only, and the majority of patients in these studies were already on background beta-blocker therapy. Data in patients with unstable angina, asymptomatic ischaemia, vasospastic angina and postmyocardial infarction are limited. Data on monotherapy with nifedipine extended release tablets are limited and based on trials of short duration (four weeks or less).

Pharmacokinetics

Absorption and Distribution
Nifedipine is almost completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero order absorption kinetics after nifedipine extended release tablet administration and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24 hour dosing interval. At steady state, the bioavailability of nifedipine extended release tablets is 86% relative to an immediate release dosage form which has a systemic availability of 45 to 68%. Administration of nifedipine extended release tablets in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced gastrointestinal retention times over prolonged periods (i.e. short bowel syndrome) may, however, influence the pharmacokinetic profile of the drug, which could result in lower plasma concentrations. The pharmacokinetics of nifedipine extended release tablets are linear over the dose range of 30 to 180 mg, in that plasma concentrations are proportional to dose administered. There is no evidence of dose dumping in either the presence or the absence of food.

Nifedipine is about 95% bound to plasma protein (albumin).

Metabolism
The active substance nifedipine is almost completely metabolised in the liver, primarily by oxidative processes (the cytochrome P450 enzyme CYP3A4). Some metabolic activity within the gut wall may also contribute to the presystemic metabolism. These metabolites show no pharmacodynamic

activity. The main metabolite is the hydroxycarbolic acid derivative (95%); the remaining 5% is the corresponding lactone.

Excretion

Nifedipine is excreted in the form of its metabolites, predominantly via the kidneys (60 to 80%), and about 5 to 15% is excreted via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1%) in the urine.

The terminal elimination half-life is 1.7 to 3.4 hours in an immediate release formulation. In cases of impaired kidney function, no substantial changes have been detected in comparison with healthy volunteers.

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.

Patients on haemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine.

Some published studies have reported slower elimination of nifedipine in different ethnic groups (e.g. Mexican, Japanese and South Asian patients). Currently, confirmatory studies only exist for the South Asian population. In comparison to Caucasian patients, there were increases in area under the curve (AUC) due to a decrease in the activity of cytochrome P450 (IIIA), while increases in Cmax were less pronounced. Elimination half-lives of both nifedipine and its pyridine metabolite were prolonged approximately twofold. Although haemodynamic responses in the South Asian healthy volunteers were similar to those reported in Caucasian patients, lower doses of nifedipine may be required in South Asian patients at the beginning of Addos XR therapy.

INDICATIONS

Treatment of hypertension. Prophylaxis of chronic stable angina pectoris.

CONTRAINDICATIONS

Known hypersensitivity to nifedipine or related dihydropyridine calcium channel blockers or to any of the excipients. Pregnancy and lactation. Cardiogenic shock. Kock pouch (ileostomy after proctocolectomy). Concomitant administration with rifampicin (see **Interactions with Other Medicines**). Within the first eight days of an acute episode of myocardial infarction.

PRECAUTIONS

Excessive hypotension. Caution should be exercised in patients with severe hypotension (systolic pressure < 90 mmHg) as there is a risk of further reduction in blood pressure.

Addos XR may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of potentiation of existing antihypertensive therapy should be noted.

Increased angina and/or myocardial infarction. Rare cases of increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase have been reported. These well documented cases are mainly in those patients who have severe obstructive coronary artery disease. The mechanism of this effect is not established.

Chest pain. There have been a small number of reports of chest pain not associated with myocardial infarction (in certain circumstances, angina pectoris-like symptoms) occurring soon after

administration of a single dose. In this case, Addos XR should be withdrawn if a causal relationship is suspected.

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 extended release tablets have no inherent antiarrhythmic action and therefore give no protection against any arrhythmias that may result from abrupt withdrawal of beta-blockers. Any such withdrawal of beta-blockers should be achieved gradually over a period of several days.

Congestive heart failure. The onset of heart failure 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.

Peripheral oedema. Mild to moderate peripheral oedema occurs in a dose dependent manner with an incidence ranging from approximately 10% with nifedipine extended release tablets 30 mg daily to about 33% at 120 mg daily. This is due to arteriolar vasodilatation and is not due to heart failure. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

Hypotension / heart rate. Because nifedipine extended release tablets are an arterial and arteriolar vasodilator, hypotension and a compensatory increase in heart rate may occur. Thus blood pressure and heart rate should be monitored carefully during nifedipine therapy. Close monitoring is especially recommended for patients who are prone to develop hypotension, those with a history of cerebrovascular insufficiency and those who are taking medications that are known to lower blood pressure.

Effect on laboratory tests. Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), AST and ALT 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*. A limited number of 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.

Acute treatment of angina pectoris. Addos XR is not suitable for the acute treatment of angina pectoris due to delayed absorption of the drug from the modified release dosage formulation.

Diabetes. Treatment with nifedipine can theoretically impair glucose metabolism, which may be of clinical relevance in some cases.

Aortic stenosis. Patients with severe aortic stenosis are at risk of developing heart failure or hypotension because of the vasodilating effects of Addos XR.

Severe gastrointestinal narrowing. As with any other nondeformable material, caution should be used when administering Addos XR to patients with a previous history of severe gastrointestinal narrowing or obstruction. Bezoars can occur in very rare cases and may require surgical intervention.

There have been rare reports of bowel obstruction requiring surgery in patients with known

oesophageal stricture, small bowel stenosis and after gastroplexy, due to the nondeformable nature of nifedipine extended release tablets. In single cases obstructive symptoms have been described without known history of gastrointestinal disorders.

Shortened transit times. The sustained release of Addos XR may be impaired in chronic diarrhoea (e.g. Crohn's disease, ulcerative colitis) or the short bowel syndrome, when the gastrointestinal transit time is less than 18 to 22 hours. Monitoring of trough blood pressure (24 hour) is advised in these patients. If control of the trough blood pressure is not satisfactory, then conventional nifedipine tablets taken twice daily should be used.

Other Nifedipine Formulations. Addos XR 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 and vice versa. Addos XR may not be bioequivalent to modified-release nifedipine preparations available overseas.

Impaired hepatic function. In patients with impaired liver function, careful monitoring and, in severe cases, a dose reduction may be necessary. The total systemic plasma clearance is reduced and elimination half-life is increased in severe liver disease.

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

Carcinogenicity.
Carcinogenesis/mutagenesis. Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic.

Effects on fertility
In isolated cases of *in vitro* fertilisation, calcium channel blockers like nifedipine have been associated with reversible biochemical changes in the head section of the spermatozoa that may result in impaired sperm function. In men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, the use of calcium channel blockers such as nifedipine should be considered as a possible cause.

Genotoxicity
In vitro and *in vivo* mutagenicity studies were negative

Use in pregnancy (Category C)
Nifedipine is contraindicated throughout pregnancy. Drugs in this class carry the potential to produce fetal hypoxia, caesarean deliveries, prematurity and intrauterine growth retardation, which may be associated with maternal hypotension.

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 has been 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.

Category C: Drugs which owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use in lactation
Nifedipine passes into the breast milk. So far, insufficient evidence is available as to whether nifedipine has an effect on breastfed infants. Breastfeeding should be stopped first if nifedipine treatment becomes necessary during the breastfeeding period.

Paediatric use
The safety and efficacy of Addos XR in children and adolescents below 18 years has not been established.

Use in the elderly
Caution should be exercised in the use of Addos XR in elderly patients, especially those with a history of hypotension or cerebrovascular insufficiency. Lower doses may be required in patients with reduced drug clearance.

INTERACTIONS WITH OTHER MEDICINES

The blood pressure lowering effect of nifedipine may be potentiated by other antihypertensive drugs.

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

Demonstrated interactions. Beta-blockers and nitrates. Although there is a possibility of additive effects with antihypertensive and negative inotropic agents, nifedipine extended release tablets may be used in conjunction with nitrates and beta-blocking drugs. Patients should be carefully monitored when such concomitant therapies are initiated.

Cimetidine. Elevation of plasma nifedipine levels during cimetidine administration has been reported. It is suggested that patients taking 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 drug and nifedipine is less pronounced.

Coumarin anticoagulants. There have been rare reports of increased prothrombin time when nifedipine was administered to patients taking coumarin anticoagulants. However, the relationship to nifedipine therapy is uncertain.

Digoxin. The simultaneous administration of nifedipine and digoxin can lead to reduced digoxin clearance and hence an increase in the plasma digoxin level. It is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing nifedipine and, if necessary, the dose of digoxin adjusted.

Quinidine. Quinidine levels have been observed to decrease upon the introduction of nifedipine and increase upon its withdrawal. For this reason, it is recommended that when nifedipine is either added to quinidine therapy or withdrawn from it, quinidine concentrations are monitored and the dose adjusted accordingly. Some authors reported increased plasma levels of nifedipine upon coadministration of both drugs, 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.

Rifampicin. Rifampicin, through its enzyme induction effect, accelerates the metabolism of nifedipine. Because this reduces the efficacy of nifedipine, the use of rifampicin in combination with nifedipine is contraindicated.

Diltiazem. Diltiazem decreases the clearance of nifedipine and hence increases plasma nifedipine levels. Therefore caution should be exercised when the two drugs are used concomitantly and a

reduction in the dose of nifedipine may be necessary.

Phenytoin. Phenytoin induces CYP3A4. Coadministration of phenytoin with nifedipine reduces the bioavailability of nifedipine. When both drugs 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 coadministration of both drugs, a reduction of the nifedipine dose should be considered when phenytoin is discontinued.

Cisapride. Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. Blood pressure should be monitored upon coadministration of both drugs, and the nifedipine dose reduced if necessary.

Theoretical potential interactions. Erythromycin. No interaction studies have been carried out between nifedipine and erythromycin. As both nifedipine and erythromycin undergo metabolism by CYP3A4, the potential for drug interaction cannot be ruled out at this stage. Erythromycin is known to inhibit CYP3A4 mediated metabolism of other drugs and could increase plasma concentrations of nifedipine if administered concomitantly.

Amprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir. A clinical study investigating the potential interaction between nifedipine and amprenavir, indinavir, nelfinavir, ritonavir or saquinavir has not yet been performed. Drugs of this class are known to inhibit the CYP3A4 system. In addition, amprenavir, indinavir, nelfinavir, ritonavir and saquinavir 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. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

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 coadministration of both medicines cannot be excluded (see **Precautions**).

Ketoconazole, itraconazole, fluconazole. A formal interaction study investigating the potential of a drug interaction between nifedipine and these drugs has not yet been performed. These drugs are known to inhibit CYP3A4. When administered orally with nifedipine, a substantial increase in systemic bioavailability of nifedipine is possible. Coadministration of these drugs with nifedipine requires careful monitoring and, if necessary, a reduction in the nifedipine dose should be considered.

Nefazadone. A clinical study investigating the potential of a drug interaction between nifedipine and nefazadone has not yet been performed. Nefazadone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon coadministration of both drugs cannot be excluded. When nefazadone is given together with nifedipine, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Candesartan cilexetil, irbesartan, doxazosin. The blood pressure lowering effect of these agents may be potentiated by coadministration 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 drug.

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 coadministration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose should be considered.

Carbamazepine, phenobarbitone. No formal studies have been performed to investigate the interaction of nifedipine with these drugs. These drugs have been shown to reduce the plasma concentrations of another dihydropyridine calcium channel blocker (nimodipine) through enzyme induction. Therefore, a decrease in the plasma concentrations of nifedipine and hence a decrease in efficacy is possible.

Sodium valproate. No formal studies have been performed to investigate the interaction of nifedipine with sodium valproate, 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 and hence an increase in efficacy is possible.

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 aspirin 100 mg on platelet aggregation and bleeding time.

Other Interactions.
Grapefruit juice.
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations of nifedipine due to a decreased first pass metabolism. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after the last ingestion of grapefruit juice.

Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine.

Laboratory tests. Barium contrast X-ray. Nifedipine extended release tablets may cause false positive findings (e.g. filling defects interpreted as polyps) when barium contrast X-ray is undertaken.

Spectrophotometric test for vanillylmandelic acid. Nifedipine may falsely increase spectrophotometric assay values of urinary vanillylmandelic acid (VMA). However measurement with high pressure liquid chromatography (HPLC) is unaffected.

Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase (AP), creatine phosphokinase (CPK), lactate dehydrogenase (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*. A limited number of 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

Clinical trial data.
The most common adverse reactions to nifedipine extended release tablets based on clinical studies sorted by CIOMS III frequency categories (n = 9,566 patients as of 13-Oct-98) are listed below.

Reactions occurring in greater than or equal to 1% and < 10% of patients.
Body as a whole. Asthenia, oedema, headache.

Cardiovascular system. Peripheral oedema, palpitation, vasodilatation.
Digestive system. Constipation.
Nervous system. Dizziness.
General disorders and administration site conditions: Feeling unwell

Reactions occurring in greater than or equal to 0.1% and < 1% of patients.
Body as a whole. Gastrointestinal and abdominal pain, chest pain, leg pain, malaise, pain.
Immune system disorders. Allergic reaction, allergic oedema/angioedema (incl. larynx oedema*)
Psychiatric disorders. Anxiety reactions, sleep disorders.
Cardiovascular system. Hypotension, postural hypotension, syncope, tachycardia.
Digestive system. Diarrhoea, dry mouth, dyspepsia, flatulence, nausea.
Hepatobiliary disorders. Transient increases in liver enzymes
Musculoskeletal system. Leg cramps, muscle cramps, joint swelling.
Nervous system. Insomnia, nervousness, paraesthesia, somnolence, vertigo, migraine, tremor.
Eye disorders. Visual disturbances
Respiratory system. Dyspnoea, nosebleed, nasal congestion.
Skin and appendages. Pruritis, rash, erythema
Urogenital system. Nocturia, polyuria.
Reproductive system and breast disorders. Erectile dysfunction
General disorders and administration site conditions. Unspecific pain, chills.

***may result in life-threatening outcome**

Reactions occurring in greater than or equal to 0.01% and < 0.1% of patients.
Body as a whole. Chest pain substernal, face oedema, fever.
Cardiovascular system. Angina pectoris (excluding unstable), cardiovascular disorder.
Digestive system. Anorexia, eructation, gastrointestinal disorder, gingivitis, gum hyperplasia, GGT increased, liver function tests abnormal, vomiting, gingival hyperplasia.
Musculoskeletal system. Arthralgia, joint disorder, myalgia.
Nervous system. Hypaesthesia, dysaesthesia.
Skin and appendages. Angioedema, maculopapular rash, pustular rash, sweating, urticaria, vesiculobullous rash.
Urogenital system. Urinary frequency.

Postmarketing reports.
The most common adverse drug reactions to nifedipine extended release tablets based on spontaneous reports, sorted by CIOMS III frequency categories (n = 2,886 reported cases as of 15-Sep-98) arelisted below.

Reactions occurring in < 0.01% of patients.
Body as a whole. Anaphylactic/anaphylactoid reaction.
Nervous system disorders. Hypoaesthesia, somnolence
Cardiac disorders. Chest Pain (angina pectoris)
Eye disorders. Eye pain
Respiratory, thoracic and mediastinal disorders. Dyspnoea
Digestive system. Bezoar, dysphagia, oesophagitis, gum disorder, intestinal obstruction, intestinal ulcer, jaundice, ALT increased, gastroesophageal sphincter insufficiency, vomiting.
Haematological and lymphatic system. Leucopenia, palpable purpure, agranulocytosis.
Metabolic and nutritional disorder. Hyperglycaemia, weight loss.
Musculoskeletal system. Muscle cramps, arthralgia, myalgia.
Skin and appendages. Exfoliative dermatitis, gynaecomastia, photosensitive dermatitis
Special senses. Blurred vision.

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

The most common adverse effect reported was oedema which was dose related and ranged in frequency from approximately 10% on 30 mg to 30% at the highest dose studied (180 mg). In clinical trials of 20 mg the frequency of peripheral oedema ranged from 0% to 4%.

There have been a small number of reports of chest pain not associated with myocardial infarction occurring soon after administration of a single dose of nifedipine. In such an event, the medicine must be discontinued if a causal relationship is suspected.

Aggravation of cardiac insufficiency has occasionally been reported in patients with compromised cardiac function or when nifedipine is given in combination with beta-blockers.

Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase (AP), creatine phosphokinase (CPK), lactate dehydrogenase (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 intrahepatic cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have also been reported.

A small (5.4%) increase in mean alkaline phosphatase has been noted in patients treated with controlled release nifedipine tablets. These cases are rare and not associated with clinical symptoms and they rarely result in values outside the normal range.

In controlled studies, controlled release nifedipine tablets did not adversely affect serum uric acid, glucose or cholesterol. Serum potassium was unchanged in patients receiving controlled release nifedipine tablets in the absence of concomitant diuretic therapy and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. A limited number of clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation in some nifedipine treated patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for this finding has been demonstrated.

In a double blind comparison of nifedipine extended release and immediate release tablets, the incidence of vasodilator reactions did not differ.

DOSAGE AND ADMINISTRATION

As far as possible the treatment must be tailored to the needs of the individual and depending on the clinical picture in each case, the basic dose must be introduced gradually. In patients with impaired liver function, careful monitoring is advised and, in severe cases, a dose reduction may be necessary.

The tablets are swallowed whole, **without chewing or being broken up**, with a little liquid, independently of mealtimes. Grapefruit juice is to be avoided.

Hypertension.

Addos XR should be initiated with 30 mg once daily. A starting dose of 20 mg may be considered when medically indicated. Monitoring of trough blood pressure should be done initially to ensure blood pressure control lasts over the dosing interval.

Depending on the severity of the disease and the patient's response, the dose can be decreased to 20 mg or increased in stages to 120 mg daily. In general, titration should proceed over a 7 to 14 day period so that the doctor can fully assess the response to each dose level and monitor the blood pressure before proceeding to higher doses. Since steady-state levels are achieved on the second day of dosing, titration may proceed more rapidly if symptoms so warrant, provided the patient is assessed frequently. Titration to doses above 120 mg/day is not recommended.

Note: Nifedipine 20 mg tablets are not available with this brand.

Chronic stable angina.
Addos XR should be initiated with 30 mg once daily. If necessary, the dosage can be increased in stages to a maximum of 90 mg once daily. Experience with doses greater than 90 mg/day in patients with angina is limited.
The initiation of Addos XR therapy in South Asian patients who have not previously taken nifedipine should start at low doses (see **Pharmacology - Pharmacokinetics**).

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

Children and adolescents
The safety and efficacy of Addos XR in children and adolescents below 18 years has not been established.

Elderly patients
Caution should be exercised in the use of Addos XR in elderly patients, especially those with a history of hypotension or cerebral vascular insufficiency. Lower doses may be required in patients with reduced drug clearance.

OVERDOSAGE

Symptoms.
The following symptoms are observed in cases of severe nifedipine intoxication: disturbances of consciousness to the point of coma, severe hypotension, tachycardic/ bradycardic heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Treatment.
As far as treatment is concerned, elimination of the poison and the restoration of stable cardiovascular conditions have priority.

After oral ingestion of a potentially dangerous amount, thorough gastric lavage is indicated, particularly in cases of intoxication with controlled release products like Addos XR. Elimination must be as complete as possible, including the irrigation of the small intestine, to prevent the subsequent absorption of the active substance. Symptoms and signs of overdose may be delayed due to the controlled release properties of these products, so patients should be kept under observation for at least 24 hours.

Haemodialysis is ineffective in removing nifedipine from the body because nifedipine is not dialysable (high plasma protein binding), but plasmaphaeresis may be considered.

Bradycardic heart rhythm disturbances may be treated symptomatically with beta-sympathomimetics and, in life-threatening situations, temporary pacemaker therapy may be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (calcium gluconate 10% solution 10 to 20 mL administered slowly intravenously and repeated if necessary). If the effects are inadequate, the treatment can be continued with ECG monitoring, with the addition of a beta-sympathomimetic drug (e.g. isoprenaline 0.2 mg slowly intravenously, repeated if necessary as a continuous infusion at 5 microgram/minute). If this is still insufficient to return the blood pressure to normal, vasoconstricting sympathomimetics such as dopamine or noradrenaline may be 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Addos XR 30 Nifedipine 30 mg. Pale red, round biconvex tablet (modified release) marked "30" on one side. Blister packs (PVC/PVDC/Al material) of 30.

Addos XR 60 Nifedipine 60 mg. Pale red, round biconvex tablet (modified release) marked "60" on one side. Blister packs (PVC/PVDC/Al material) of 30.

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

30th November 2004 (Addos XR 30)
14th February 2005 (Addos XR 60)

DATE OF MOST RECENT AMENDMENT

23rd May 2016