

Arrow - Nifedipine XR

Nifedipine extended release tablets

Presentation

Arrow - Nifedipine XR is an extended release (XR) formulation.

Arrow - Nifedipine XR 30 Pale red, round biconvex tablet marked "30" on one side. Each tablet contain 30 mg of nifedipine.

Arrow - Nifedipine XR 60 Pale red, round biconvex tablet marked "60" on one side. Each tablet contain 60 mg of nifedipine.

Clinical Particulars

Actions

Nifedipine is a calcium ion influx inhibitor, also known as calcium channel blocker or calcium antagonist. It inhibits the transmembranal influx of calcium ions into cardiac and vascular smooth muscle cells. 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, which is an underlying cause of hypertension, results from an elevation of 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

In the multicenter, randomized, placebo controlled, double blind ACTION trial with a follow-up of 5 years involving 7,665 patients with stable angina pectoris on best practice standard treatment, the effects on clinical outcomes of nifedipine extended release tablets versus 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 nifedipine extended release tablets (n = 3,825) and patients allocated placebo (n = 3,840) (P = 0.54).

In a predefined subgroup analysis which included 3,997 angina patients with hypertension at baseline, nifedipine extended release tablets led to a significant 13% reduction of the primary endpoint for efficacy.

Nifedipine extended release tablets 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).

Nifedipine extended release tablets 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).

Pharmacokinetics

Nifedipine is almost completely absorbed after oral administration. After administering nifedipine extended release tablets, plasma drug concentrations rise at a gradual, controlled rate exhibiting zero order absorption kinetics and reach a plateau at approximately 6 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 that 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.

Distribution

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

Biotransformation

The active substance nifedipine is almost completely metabolised in the liver, primarily by oxidative processes (via cytochrome P450 enzyme CYP3A4). Some metabolic activity within the gut wall may also contribute to the pre-systemic metabolism. These metabolites show no pharmacodynamic activity. The main metabolite is the hydroxycarboxylic acid derivative (95%), while the remaining is the corresponding lactone.

Elimination

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 due to a decrease in the activity of cytochrome P450 (III A), while increases in C_{max} 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 Arrow - Nifedipine XR therapy.

Indications

Treatment of mild to moderate hypertension.

Prophylaxis of chronic stable angina pectoris (angina of effort).

Dosage and Administration

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. In patients with impaired liver function, careful monitoring is advised. In severe cases, a dose reduction may be necessary.

Co-administration 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 **Interactions**).

The tablets are swallowed whole with a little liquid, independently of meals. Do not chew, halve or break up the tablets. Grapefruit juice is to be avoided (see **Interactions**).

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Hypertension

Arrow - Nifedipine XR should be initiated with 30 mg once daily. 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 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.

Chronic stable angina pectoris

Arrow - Nifedipine 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 Arrow - Nifedipine XR therapy in South Asian patients who have not previously taken nifedipine should start at low doses (see **Pharmacokinetics**).

Duration of treatment

The attending doctor will determine the duration of use.

Contraindications

Known hypersensitivity to nifedipine or related dihydropyridine calcium channel blockers.

Pregnancy before week 20 and lactation.

Cardiogenic shock.

Within the first eight days of an acute episode of myocardial infarction.

Kock pouch (ileostomy after proctocolectomy).

Concomitant administration with rifampicin (see **Interactions**).

Warnings and Precautions

Excessive hypotension

Due to a risk of further reduction in blood pressure with nifedipine, caution should be exercised in patients with severe hypotension (systolic pressure < 90 mmHg) in case of manifesting heart failure and in the case of severe aortic stenosis.

Nifedipine 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.

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

Hypotension and heart rate

Because nifedipine is 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.

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, nifedipine should be withdrawn if a causal relationship is suspected.

Acute treatment of angina pectoris

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

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 tablet 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.

Aortic stenosis

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

Cardiac insufficiency

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

Diabetes

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

Shortened transit times

The sustained release of Arrow - Nifedipine 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 hours) 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

Arrow - Nifedipine XR tablets are not bioequivalent to immediate release nifedipine capsules or tablets. Patients should be carefully monitored if it is decided to switch between immediate release and extended release nifedipine, or vice versa.

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.

Beta-blocker withdrawal

Nifedipine has no inherent anti-arrhythmic action and therefore gives 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.

Cytochrome P450 3A4 system

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 **Interactions**). Drugs, which are weak to moderate inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, for example, macrolide antibiotics, anti-HIV protease inhibitors, azole anti-mycotics, some antidepressants, quinupristin and dalfopristin, valproic acid and cimetidine (see **Interactions**). Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Laboratory tests

Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase (5.4%), creatine phosphokinase, lactate dehydrogenase, aspartate amino transferase and alanine amino transferase 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.

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

Carcinogenesis and mutagenesis

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 (see **Preclinical Safety Data**).

Impairment of 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.

Use in pregnancy (Category C)

Nifedipine is contraindicated in pregnancy before week 20. Drugs in this class carry the potential to produce foetal hypoxia associated with maternal hypotension. Also, there are no safety and efficacy data from well controlled studies in pregnant women.

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

From the clinical evidence available, a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean 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 administering nifedipine with intravenous magnesium sulphate, owing to the

possibility of an excessive fall in blood pressure which could harm both mother and foetus.

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.

Use in the elderly

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

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.

Adverse Effects

Adverse drug reactions 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:

Adverse drug reactions listed under "common" were observed with a frequency below 3%, with the exception of oedema (9.9%) and headache (3.9%).

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

Post-marketing reports

The adverse drug reactions to nifedipine extended release tablets, based on spontaneous reports sorted by CIOMS III categories of frequency and (n = 2886 reported cases calculated on patient exposure, as of 15th September 1998) are listed below.

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).

Clinical Description	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%	Very Rare <0.01%
Immune System Disorders				
Acute hypersensitivity reactions		Allergic reaction Allergic oedema angioedema	Pruritus Urticaria Rash	Anaphylactic or anaphylactoid reaction
Psychiatric Disorders				
Behavioural disturbances and sleep disorders		Anxiety reactions Sleep disorders		
Nervous System Disorders				
Unspecific cerebrovascular symptoms	Headache	Vertigo Migraine		
Unspecific neurological symptoms		Dizziness Tremor		
Unspecific altered peripheral perception			Paraesthesia Dysaesthesia	
Eye Disorders				
Unspecific eye disorders		Visual disturbances		
Cardiac Disorders				
Unspecific arrhythmias		Tachycardia Palpitations		
Vascular Disorders				
Unspecific vascular symptoms	Oedema Vasodilatation	Hypotension Syncope		

Respiratory Disorders				
Upper respiratory tract symptoms		Nosebleed Nasal congestion		Dyspnoea
Gastrointestinal Disorders				
Gastrointestinal symptoms	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Bezoars, intestinal obstruction (depending on tablet formulation) Dysphagia Intestinal ulcer Vomiting
Hepatobiliary Disorders				
Mild to moderate hepatic reactions		Transient increase in liver enzymes		
Skin and Subcutaneous Tissue Disorders				
Unspecific skin reactions		Erythema		
Musculoskeletal and Connective Tissue Disorders				
Unspecific joint and muscular disorders		Muscle cramps Joint swelling		
Renal and Urinary Disorders				
Urinary disorders		Polyuria Dysuria		
Reproductive System Disorders				
Sexual dysfunction		Erectile dysfunction		

General Disorders and Administration Site Conditions				
General feeling of illness	Feeling unwell	Unspecific pain Chills		

Interactions

Drugs that affect nifedipine

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.

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. With co-administration of rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see **Contraindications**).

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

Macrolide antibiotics

No interaction studies have been carried out between nifedipine and macrolide antibiotics (e.g. erythromycin). Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore, the potential for an increase of nifedipine plasma concentrations with co-administration of erythromycin cannot be excluded (see **Warnings and Precautions**).

Azithromycin, although structurally related to the class of macrolide antibiotics, is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors

A clinical study investigating the potential interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class (e.g. amprenavir, indinavir, nelfinavir, ritonavir and saquinavir) are known to inhibit the CYP3A4 system and 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 (see **Warnings and Precautions**).

Azole anti-mycotics

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 (e.g. ketoconazole, itraconazole or fluconazole) are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to an increased absorption cannot be excluded (see **Warnings and 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 the CYP3A4 mediated metabolism of other drugs. Therefore, an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (see **Warnings and Precautions**).

Quinupristin and dalfopristin

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

Valproic acid

No formal studies have been performed to investigate the interaction of nifedipine with valproic acid (sodium valproate). As valproic acid has been shown to increase the plasma concentrations of another dihydropyridine calcium channel blocker (nimodipine) through enzyme inhibition, an increase in the plasma concentrations of nifedipine and hence an increase in efficacy is possible (see **Warnings and Precautions**).

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (see **Warnings and Precautions**). 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.

Cisapride

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

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

Phenytoin

Phenytoin induces CYP3A4. Co-administration 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 co-administration of both drugs, a reduction of the nifedipine dose should be considered when phenytoin is discontinued.

Carbamazepine and phenobarbitone

No formal studies have been performed to investigate the interaction of nifedipine with carbamazepine or phenobarbitone. However, 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.

Effects of nifedipine on other drugs

Blood pressure lowering drugs

Nifedipine may increase the blood pressure lowering effect of concomitant administered antihypertensive drugs and those drugs known to cause hypotension. The examples are diuretics, beta-blockers, nitrates, ACE inhibitors, angiotensin AT₁ receptor blockers, other calcium antagonists, α -adrenergic blocking agents, PDE5 inhibitors and α -methyldopa. The antihypertensive actions of nifedipine may be potentiated with co-administration of these drugs.

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, since severe hypotension can occur.

Deterioration of heart failure is also known to develop in isolated cases when nifedipine is co-administered with beta-blockers.

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.

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.

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 to monitor the digoxin levels when initiating, adjusting and discontinuing nifedipine, and to check the patient for symptoms of digoxin toxicity. If necessary, the dose of digoxin should be adjusted.

Quinidine

Quinidine levels have been observed to decrease upon the introduction of nifedipine and increase upon its withdrawal. Thus, it is recommended that when nifedipine is either added to quinidine therapy or withdrawn from it, quinidine concentrations are monitored and its dose is adjusted accordingly.

Some authors reported increased plasma levels of nifedipine upon co-administration 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.

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

Magnesium sulfate (parenteral)

Nifedipine increases effects of parenteral magnesium sulfate and risk of hypotension. Care must be exercised in pregnant women when such combination is used. Consider reducing magnesium sulfate dosage, close monitoring of blood pressure, deep tendon reflexes and respiratory function.

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.

Drug-food interactions

Grapefruit juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice results in elevated plasma concentrations and prolonged action of nifedipine due to an increase of drug bioavailability. As a consequence, the blood pressure lowering effect may be increased.

Ingestion of grapefruit or grapefruit juice should therefore be avoided while taking nifedipine.

Interactions shown not to exist

Concomitant administration of the following drugs has been shown not to interfere with the pharmacokinetic properties of either nifedipine or vice versa: ajmalin, aspirin*, benazepril, candesartan cilexetil, cerivastatin, debrisoquine, doxazosin, irbesartan, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone, talinolol and triamterene hydrochlorothiazide.

* Nifedipine did not have clinically significant effects on the actions of aspirin 100 mg on platelet aggregation and bleeding time.

Other forms of interactions

Barium contrast X-ray

Nifedipine extended release tablets (depending on the formulations) 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. However, measurement with high performance liquid chromatography is unaffected.

Overdosage

Symptoms

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

Treatment

As far as treatment is concerned, elimination of the active substance 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 extended release products like Arrow - Nifedipine 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 extended 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 with relatively low volume of distribution), but plasmapheresis 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 (10 to 20 mL of a 10% calcium gluconate solution for slow intravenous administration, and repeat 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 for slow intravenous administration, and repeat 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 added. 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.

Pre-clinical Safety Data

Acute toxicity

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

* 95% confidence level

Subacute and subchronic toxicity

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

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

Chronic toxicity

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

Carcinogenicity

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic.

Mutagenicity

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

Reproduction toxicology

Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies. 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 foetal 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.

Pharmaceutical Precautions

Storage

Store in a cool, dry place where it stays below 25 °C.

Shelf-life

36 months

Medicine Classification

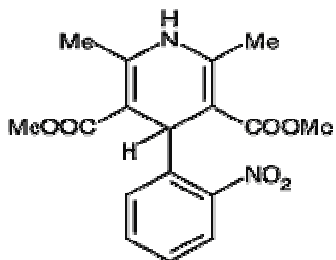
Prescription medicine

Package Quantities

Arrow - Nifedipine XR 30 and Arrow - Nifedipine XR 60 are both available in blister packs of 30 tablets.

Further Information

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



$C_{17}H_{18}N_2O_6$

Molecular weight: 346.3

CAS No.: 21829-25-4

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

The tablets also contain the following excipients: purified talc, povidone, lactose, carbomer 934P, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, iron oxide red C177491, macrogol 4000 and Eudragit E100. The tablets are gluten free.

Name and Address

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Date of Preparation

20 August 2010