NEW ZEALAND DATA SHEET

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.

Indications

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

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.

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

For coronary heart disease:

Chronic stable angina pectoris (angina of effort) Arrow - Nifedipine XR 30 tablet once daily (1 x 30 mg/day)
Arrow - Nifedipine XR 60 tablet once daily (1 x 60 mg/day)

For hypertension:

Arrow - Nifedipine XR 30 tablet once daily (1 x 30 mg/day)
Arrow - Nifedipine XR 60 tablet once daily (1 x 60 mg/day)
In general, therapy should be initiated with 30 mg once daily.

Coadministration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the Arrow - Nifedipine XR or not to use Arrow - Nifedipine XR at all (see Interactions).

Duration of Treatment

The attending doctor will determine the duration of use.

Method of Administration

As a rule the tablets are swallowed whole with a little liquid, irrespective of meal times. Grapefruit juice is to be avoided (see Interactions). The tablets are swallowed whole with a little liquid, independently of meals.

The tablets must not be chewed or broken up!

Additional information on special populations

Children and adolescents

The safety and efficacy of Arrow - Nifedipine XR in children below 18 years has not been established.

Geriatric patients

Based on the pharmacokinetic data for Arrow - Nifedipine XR, no dose adaptation in elderly people above 65 years is necessary.

Patients with hepatic impairment

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

Patients with renal impairment

Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (see Pharmacokinetic Properties).

Contraindications

Arrow - Nifedipine XR must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients (see Excipients).

Arrow - Nifedipine XR is contraindicated in pregnancy before week 20 and during breastfeeding (see Pregnancy and Lactation).

Arrow - Nifedipine XR must not be used in cases of cardiovascular shock.

Arrow - Nifedipine XR must not be used in patients with Kock pouch (ileostomy after proctocolectomy).
Arrow - Nifedipine XR must not be used in combination with rifampicin because efficient plasma levels of nifedipine may not be obtained due to enzyme induction (see Interactions)

**Warnings and Precautions**

Care must 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.

There are no safety and efficacy data from well-controlled studies in pregnant women.

Animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects (see Pre-clinical 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 deliveries 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, when administering Arrow - Nifedipine XR with intravenous magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and fetus.

As with other non-deformable material care should be used when administering Arrow - Nifedipine XR in patients with pre-existing severe gastrointestinal narrowing because obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention.

In single cases obstructive symptoms have been described without known history of gastrointestinal disorders.

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

In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary (see Pharmacokinetic Properties).
Nifedipine extended release tablets are not bioequivalent to immediate release nifedipine capsules and tablets. Patients should be carefully monitored if it is decided to switch between immediate release and modified release nifedipine or vice versa.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Medicines 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).

Medicines, which are inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are,

- macrolide antibiotics (e.g., erythromycin),
- anti-HIV protease inhibitors (e.g., ritonavir),
-azole antymycotics (e.g., ketoconazole),
- the antidepressants nefazodone and fluoxetine,
- quinupristin/dalfopristin,
- valproic acid,
- cimetidine.

Upon co-administration with these medicines, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Dose titration up to the maximal daily dose of 120 mg nifedipine may result in a maximal uptake of (2 mmol sodium) per day. This should be taken into consideration for patients on a controlled sodium diet.

For use in special populations, see Dosage and Administration.

**PREGNANCY AND LACTATION**

*Pregnancy (Category C)*

Nifedipine is contraindicated in pregnancy before week 20. (See Contraindications)

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

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after end of the organogenesis period.
Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and under developed 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 at several times the recommended maximum dose for humans.

**In vitro Fertilisation**

In single 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 those 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.

**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.

**Effect on Ability to Drive and Use Machines**

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.

**For use in special populations, see Dosage and Method of Administration.**

**Interactions**

*Medicines that affect nifedipine*

Nifedipine is metabolised via the cytochrome P450 CYP3A4 system, located in the intestinal mucosa and the liver. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see Warnings and Precautions).

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

**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 (e.g. erythromycin)**

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 both medicines 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 (e.g. ritonavir)**

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 Cytochrome P450 3A4 system. In addition, medicines of this class have been shown to inhibit *in vitro* the Cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first-pass metabolism and a decreased elimination cannot be excluded (see **Warnings and Precautions**).

**Azole anti-mycotics (e.g., ketoconazole)**

A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. Medicines of this class 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**).

**Fluoxetine**

A clinical study investigating the potential of a drug interaction between Adalat OROS and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both medicines 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 Cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, an increase of nifedipine plasma concentrations upon co-administration of both medicines 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 and valproic acid. 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).

**Further Studies**

**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**

A formal interaction study investigating the potential of a drug interaction between nifedipine and phenytoin has not yet been performed. However, phenytoin is known as a potential inducer of the cytochrome P450 3A4 system. Furthermore, concomitant administration of phenytoin and drugs structurally related to nifedipine clearly reduced their bioavailability. Thus a clinically relevant reduction of the bioavailability of nifedipine cannot be excluded.

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

**Effects of nifedipine on other medicines**

**Blood pressure lowering medicines**

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

- diuretics,
- β-blockers,
- ACE-inhibitors,
- angiotensin 1 (AT1) receptor-antagonists,
- other calcium antagonists,
- α-adrenergic blocking agents,
- PDE5 inhibitors,
- α-methyldopa.

**Beta-blockers and nitrates**

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

**Digoxin**

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

**Quinidine**

When nifedipine and quinidine have been administered simultaneously, occasionally lowered quinidine plasma concentrations have been observed in individual cases. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of nifedipine. Also in some cases after the discontinuation of nifedipine a distinct increase in plasma concentrations of quinidine have been noted. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose is recommended.
**Diltiazem**

Diltiazem decreases the clearance of nifedipine. The combination of both medicines should be administered with caution and a reduction of the nifedipine dose may be considered.

**Tacrolimus**

Tacrolimus is metabolised by Cytochrome P450 3A4 system. Data recently published indicate that the dose of nifedipine administered simultaneously with tacrolimus may be reduced in individual cases. With co-administration of tacrolimus, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose should be considered.

**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.

**Interactions with other medicinal products**

The blood pressure lowering effect of Adalat OROS may be potentiated with coadministration of other antihypertensive medicines.

**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. 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 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 interaction**

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

**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 frequencies of ADRs reported with nifedipine containing products are summarised in Table 1 below. With each frequency grouping, ADRs are presented in order of decreasing seriousness.

The frequencies of ADRs are defined as:

- **Common:** \( \geq 1/100 \text{ to } < 1/10 \) (\( \geq 1\% \text{ to } <10\% \))
- **Uncommon:** \( \geq 1/1000 \text{ to } < 1/100 \) (\( \geq 0.1\% \text{ to } <1\% \))
- **Rare:** \( \geq 1/10000 \text{ to } < 1/1000 \) (\( \geq 0.01\% \text{ to } <0.1\% \))

---

Page 10 of 19
Table 1. Adverse Drug Reactions reported based on clinical trial data

<table>
<thead>
<tr>
<th>Clinical Description</th>
<th>Common ≥1% to &lt;10%</th>
<th>Uncommon ≥0.1% to &lt;1%</th>
<th>Rare ≥0.01% to &lt;0.1%</th>
<th>Very Rare &lt;0.01%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hypersensitivity reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergic reaction</td>
<td>Allergic oedema angioedema (including larynx oedema)</td>
<td>Pruritus Urticaria Rash</td>
<td>Anaphylactic or anaphylactoid reaction</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural disturbances and sleep disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety reactions</td>
<td>Sleep disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific cerebrovascular symptoms</td>
<td>Headache</td>
<td>Vertigo Migraine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unspecific neurological symptoms</td>
<td></td>
<td>Dizziness Tremor</td>
<td></td>
</tr>
<tr>
<td>Unspecific altered peripheral perception</td>
<td></td>
<td></td>
<td></td>
<td>Paraesthesia Dysaesthesia</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific eye disorders</td>
<td></td>
<td></td>
<td>Visual disturbances</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific arrhythmias</td>
<td></td>
<td></td>
<td>Tachycardia Palpitations</td>
<td></td>
</tr>
<tr>
<td>Clinical Description</td>
<td>Common ≥1% to &lt;10%</td>
<td>Uncommon ≥0.1% to &lt;1%</td>
<td>Rare ≥0.01% to &lt;0.1%</td>
<td>Very Rare &lt;0.01%</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific vascular symptoms</td>
<td>Odema Vasodilatation</td>
<td>Hypotension Syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract symptoms</td>
<td>Nosebleed Nasal congestion</td>
<td></td>
<td>Dyspnoea</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Constipation</td>
<td>Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth</td>
<td>Gingival hyperplasia</td>
<td>Bezoars, intestinal obstruction (depending on tablet formulation) Dysphagia Intestinal ulcer Vomiting</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate hepatic reactions</td>
<td></td>
<td>Transient increase in liver enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific skin reactions</td>
<td></td>
<td>Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific joint and muscular disorders</td>
<td>Muscle cramps Joint swelling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary disorders</td>
<td>Polyuria Dysuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Description</td>
<td>Common ≥1% to &lt;10%</td>
<td>Uncommon ≥0.1% to &lt;1%</td>
<td>Rare ≥0.01% to &lt;0.1%</td>
<td>Very Rare &lt;0.01%</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Reproductive System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Erectile dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General feeling of illness</td>
<td>Feeling unwell</td>
<td>Unspecific pain</td>
<td>Chills</td>
<td></td>
</tr>
</tbody>
</table>

* = may result in life-threatening outcome

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

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 adverse effects**

The ADRs identified during the ongoing market surveillance and for which a frequency could be not estimated are: agranulocytosis, leukopaenia, anaphylactic/anaphylactoid reaction, hyperglycaemia, hypoaesthesia, somnolence, eye pain, chest pain (angina pectoris), dyspnoea, bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting, gastrooesophageal sphincter insufficiency, jaundice, toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura, arthralgia and myalgia.

**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, tachycardic/bradycardic heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

**Management of Overdose**

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

After oral ingestion thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.
Particularly in cases of intoxication with slow-release products like nifedipine 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 can be advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10 to 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 an insufficient increase in blood pressure is achieved with calcium, 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.

**Pharmacodynamic Properties**

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In the heart nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of partially stenosed areas. Further, nifedipine reduces the vascular smooth muscle tone in the coronary arteries and prevents vasospasm. The end-result is an increased poststenotic blood flow and an increased oxygen supply. Parallel to this, nifedipine reduces the oxygen requirement by lowering peripheral resistance (afterload). With long-term use nifedipine can also prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine reduces the smooth muscle tone of the arterioles, thus lowering the increased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex increase in heart rate and thus in the cardiac output. However, this increase is not enough to compensate for the vasodilation. In addition nifedipine increases sodium and water excretion both in the short-term and long-term use. The
blood-pressure-lowering effect of nifedipine is particularly pronounced in hypertensive patients.

In the multicenter, randomised, placebo-controlled, double-blind ACTION trial with a follow-up of 5 years involving 7665 patients with stable angina pectoris on best practice standard treatment, the effects on clinical outcomes of nifedipine extended release tablets vs placebo were investigated.

The primary endpoint for efficacy (combined rate of death from any cause, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularisation) did not differ between patients assigned nifedipine extended release tablets (n=3825) and patients allocated placebo (n=3840) \( (P=0.54) \).

In a predefined subgroup analysis which included 3997 angina patients with hypertension at baseline 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, revascularisation, 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 extended release tablet 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 extended release tablet group compared to placebo. The outcome of the third secondary endpoint ‘major cardiovascular event’ did not show differences between the two treatment groups \( (P=0.26) \).

**Pharmacokinetic Properties**

Nifedipine extended release tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours.

**Absorption**

After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations is 45 to 56% owing to a first pass effect. At steady-state the bioavailability of nifedipine extended release tablets ranges from 68 to 86% relative to Nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption, but does not influence the extent of drug availability.
Plasma drug concentrations rise at a controlled rate after nifedipine extended release tablet dose and reach a plateau at approximately 6 to 12 hours after the first dose. Following multiple days of dosing, relatively constant plasma concentrations at this niveau are maintained with minimum peak to trough fluctuations over a 24 hours dosing interval (0.9 to 1.2 ng/mL).

Table 2 shows the peak plasma concentrations ($C_{\text{max}}$) of nifedipine extended release tablets and the time to reach the peak plasma concentrations ($t_{\text{max}}$):

**Table 2. Peak plasma concentrations and time to reach peak plasma concentrations**

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$t_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine 30 mg</td>
<td>20-21</td>
<td>12-15*</td>
</tr>
<tr>
<td>extended release tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine 30 mg</td>
<td>43 – 55</td>
<td>7 - 9</td>
</tr>
<tr>
<td>extended release tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*not pronounced due to plateau - like plasma concentration time course

**Distribution**

Nifedipine is about 95 % bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

**Biotransformation**

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

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

**Elimination**

The terminal elimination half-life is 1.7 to 3.4 hours in conventional formulations (Nifedipine capsules). The terminal half-life after nifedipine extended release tablets does not represent a meaningful parameter as a plateau- like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of last dose, the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

In cases of impaired kidney function, no substantial changes have been detected in comparison with healthy volunteers.
In cases of impaired liver function, the total clearance is reduced. A dose reduction may be necessary in severe cases (see **Warnings and Precautions**).

---

**Pre-clinical Safety Data**

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

**Acute toxicity**

Acute toxicity has been investigated in various animal species and the individual results are listed in Table 3:

**Table 3. Acute toxicity in various animal species**

<table>
<thead>
<tr>
<th></th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>oral</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
<td>494 (421-572)*</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td>1022 (950-1087)*</td>
</tr>
<tr>
<td><strong>Rabbit</strong></td>
<td>250-500</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td>~100</td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td>&gt;250</td>
</tr>
</tbody>
</table>

* 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 parental (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**

A long-term study in rats (2 years) yielded no evidence of a carcinogenic effect of nifedipine.
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, mice and rabbits, including digital anomalies malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow but have also been observed in animals treated with nifedipine solely after end of the organogenesis period. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits) and prolonged pregnancy/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 at 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:

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{MeOOC} & \quad \text{Me} \\
\text{H} & \quad \text{NO}_2 \\
\text{MeOOC} & \quad \text{Me}
\end{align*}
\]

C_{17}H_{18}N_{2}O_{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.

Excipients

The tablets also contain the following excipients: purified talc, povidone, lactose, carbomer 934P, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, iron oxide red CI77491, macrogol 4000 and Eudragit E100. The tablets are gluten free.

Name and Address

Actavis New Zealand Limited
Mount Eden Central Business Park
33a Normanby Road, Mt. Eden
Auckland, New Zealand

Date of Preparation

1 July 2013