

ADEFIN XL



1. Product Name

ADEFIN XL, 30 mg and 60 mg modified release tablets.

2. Qualitative and Quantitative Composition

Each ADEFIN XL 30 mg modified release tablet contains 30 mg of nifedipine.

Each ADEFIN XL 60 mg modified release tablet contains 60 mg of nifedipine.

Excipients with known effect:

Each ADEFIN XL 30 mg modified release tablet contains 23.9 mg sodium chloride, see section 4.4.

Each ADEFIN XL 60 mg modified release tablet contains 47.8 mg sodium chloride, see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

ADEFIN XL 30 mg tablet: Round, pink, biconvex coated tablet marked with "30" on one side.

ADEFIN XL 60 mg tablet: Round, pink, biconvex coated tablet marked with "60" on one side.

4. Clinical Particulars

4.1 Therapeutic indications

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

4.2 Dose and method of administration

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

Dose

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 One ADEFIN XL 30 tablet once daily

(angina of effort)	(1 x 30 mg/day) One ADEFIN XL 60 tablet once daily (1 x 60 mg/day)
For hypertension:	One ADEFIN XL 30 tablet once daily (1 x 30 mg/day) One ADEFIN XL 60 tablet once daily (1 x 60 mg/day)

In general, therapy should be initiated with 30 mg once daily.

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 section 4.5).

The attending doctor will determine the duration of use.

Special populations

Elderly

Based on the pharmacokinetic data for nifedipine, no dose adaptation in elderly people above 65 years is necessary.

Renal impairment

Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4 and section 5.2).

Paediatric

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

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 section 4.5).

The tablets must not be chewed or broken up.

Do not halve ADEFIN XL tablets.

4.3 Contraindications

ADEFIN XL tablets must not be used:

- in cases of known hypersensitivity to nifedipine or to any of the excipients listed in section 6.1;
- in cases of cardiovascular shock;
- in patients with Kock pouch (ileostomy after proctocolectomy);
- in combination with rifampicin, because efficient plasma levels of nifedipine may not be obtained due to enzyme induction (see section 4.5).

ADEFIN XL tablets are contraindicated in pregnancy before week 20 and during breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 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 section 5.3) 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, also when administering nifedipine modified release tablets with intravenous magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and foetus.

As with other non-deformable material care should be used when administering nifedipine modified release tablets 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 modified release tablets may cause false positive effects (e.g. filling defects interpreted as polyp).

In patients with mild, moderate or severe impaired liver function careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.2 and section 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine modified 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 section 4.5).

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

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

Upon co-administration with these 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 section 4.2.

4.5 Interaction with other medicines and other forms of interaction

Medicines that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in 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 intestinal mucosa and in 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 section 4.4).

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 section 4.3)

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 section 4.2).

Macrolide antibiotics (e.g. erythromycin)

No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, the potential for an increase of nifedipine plasma concentrations with co-administration of both medicines cannot be excluded (see section 4.4).

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 of a drug 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 concentration of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded (see section 4.4).

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 section 4.4).

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* cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore, an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded (see section 4.4).

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 section 4.4).

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine, with the effect varying markedly between individuals (see section 4.4).

Valproic Acid

No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded (see section 4.4).

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (see section 4.4).

Further studies

Cisapride

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

Cytochrome P450 3A4 system-inducing anti-epileptic medicines, 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 of the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both medicines, a reduction of the nifedipine dose should be considered when the treatment with phenytoin is discontinued.

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both 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 anti-hypertensives, such as:

- diuretics
- β -blockers
- ACE-inhibitors
- angiotensin II receptor-antagonists
- other calcium antagonists
- α -adrenergic blocking agents
- PDE5 inhibitors
- α -methyldopa.

When nifedipine is administered simultaneously with β -receptor blockers the patient should be carefully monitored, since 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 has been shown to be metabolised via the 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 considered.

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 / grapefruit juice should therefore be avoided while taking nifedipine (see section 4.2).

Interactions shown not to exist

Ajmaline

Concomitant administration of nifedipine and ajmaline has no effect on the metabolism of ajmaline.

Aspirin

Concomitant administration of nifedipine and aspirin 100 mg has no effect on the pharmacokinetics of nifedipine. Co-administration of nifedipine does not alter the effect of aspirin 100 mg on the platelet aggregation and bleeding time.

Benazepril

Concomitant administration of nifedipine and benazepril has no effect on the pharmacokinetics of nifedipine.

Candesartan cilexetil

Concomitant administration of nifedipine and candesartan cilexetil has no effect on the pharmacokinetics of either medicine.

Debrisoquine

Concomitant administration of nifedipine and debrisoquine has no effect on the metabolic ratio of debrisoquine.

Doxazosin

Concomitant administration of nifedipine and doxazosin has no effect on the pharmacokinetics of nifedipine.

Irbesartan

Concomitant administration of nifedipine and irbesartan has no effect on the pharmacokinetics of irbesartan.

Omeprazole

Concomitant administration of nifedipine and omeprazole has no clinically relevant effect on the pharmacokinetics of nifedipine.

Orlistat

Concomitant administration of nifedipine and orlistat has no effect on the pharmacokinetics of nifedipine.

Pantoprazole

Concomitant administration of nifedipine and pantoprazole has no effect on the pharmacokinetics of nifedipine.

Ranitidine

Concomitant administration of nifedipine and ranitidine has no effect on the pharmacokinetics of nifedipine.

Rosiglitazone

Concomitant administration of nifedipine and rosiglitazone has no clinically relevant effect on the pharmacokinetics of nifedipine.

Talinolol

Concomitant administration of nifedipine and talinolol has no effect on the pharmacokinetics of nifedipine.

Triamterene hydrochlorothiazide

Concomitant administration of nifedipine and triamterene hydrochlorothiazide has no effect on the pharmacokinetics of nifedipine.

Other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Nifedipine is contraindicated in pregnancy before week 20 (see section 4.3).

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

In animal studies, nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity (see section 5.3).

Breast-feeding

Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

Fertility

In single cases of *in vitro* fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes (see section 5.3).

4.7 Effects on ability to drive and use machines

Reactions to the medicine, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery (see section 4.8). This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

4.8 Undesirable effects

Summary of the safety profile

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).

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency from clinical trial data are listed below:

The frequencies of ADRs are defined as:

Common	≥ 1/100 to < 1/10 (≥ 1% to <10%)
Uncommon	≥ 1/1000 to < 1/100 (≥ 0.1% to <1%)
Rare	≥ 1/10000 to < 1/1000 (≥ 0.01% to <0.1%)

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

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

Table 1. Adverse drug reactions reported based on clinical trial data

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Immune system disorders			
Acute hypersensitivity reactions		Allergic reaction Allergic oedema / angioedema (including larynx oedema*)	Pruritus Urticaria Rash
Psychiatric disorders			
Behavioural disturbances and sleep disorders		Anxiety reactions Sleep disorders	
Nervous system disorders			
Unspecific cerebro-vascular symptoms	Headache	Vertigo Migraine	
Unspecific neurological symptoms		Dizziness Tremor	
Unspecific altered peripheral perception			Par-/Dysaesthesia
Eye disorders			
Unspecific eye disorders		Visual disturbances	
Cardiac disorders			
Unspecific arrhythmias		Tachycardia Palpitations	
Vascular disorders			
Unspecific vascular symptoms	Oedema Vasodilatation	Hypotension Syncope	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract symptoms		Nosebleed Nasal congestion	
Gastrointestinal disorders			
Gastrointestinal symptoms	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia
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	

Clinical description	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Renal and urinary disorders			
Urinary disorders		Polyuria Dysuria	
Reproductive system and breast disorders			
Sexual dysfunction		Erectile dysfunction	
General disorders and administration site conditions			
General feeling of illness	Feeling unwell	Unspecific pain Chills	

* = 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.

Post marketing adverse effects

The ADRs identified during the ongoing market surveillance and for which a frequency could be not estimated are: agranulocytosis, leukopenia, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>.

4.9 Overdose

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac/bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

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 ADEFIN XL 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.

For advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives.

ATC code: C08CA05

Mechanism of action

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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 modified 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 modified release tablets led to a significant 13% reduction of the primary endpoint for efficacy.

Nifedipine modified 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 modified 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 modified 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 modified 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 ($p=0.26$).

5.2 Pharmacokinetic properties

ADEFIN XL tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45 to 56% owing to a first pass effect. At steady-state the bioavailability of nifedipine modified 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 modified 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 nanograms/mL).

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

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

	C_{max} (nanograms/mL)	t_{max} (h)
Nifedipine 30 mg modified release tablets	20 - 21	12 - 15 *
Nifedipine 60 mg modified release tablets	43 - 55	7 - 9 *

* 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 pharmacodynamic 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 modified 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 a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and C_{max} of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4).

5.3 Preclinical safety data

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

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

	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 parenteral (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 foetotoxic 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 foetotoxic effects in animals were maternally toxic at several times the recommended maximum dose for humans.

6. Pharmaceutical Particulars

6.1 *List of excipients*

- Hypromellose
- Polyethylene oxide
- Magnesium stearate
- Sodium chloride
- Iron oxide red (E172/CI 77491)
- Cellulose acetate
- Macrogol 3350
- Hydroxypropyl cellulose
- Propylene glycol
- Titanium dioxide (E171/CI 77891)
- Black printing ink

ADEFIN XL is lactose, gluten and sugar free.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

4 years for ADEFIN XL 30 mg in in blister packs (Al/PVC/PVDC or PP/Al).

5 years for ADEFIN XL 30 mg in in blister packs (Aclar/Al/PVC).

4 years for ADEFIN XL 60 mg in in blister packs (PA/Al/PVC or Al/PVC/PVDC).

5 years for ADEFIN XL 60 mg in in blister packs (Aclar/Al/PVC or PP/Al).

6.4 *Special precautions for storage*

Store at or below 25°C for ADEFIN XL in in blister packs (PP/Al).

Store at or below 30°C for ADEFIN XL in in blister packs (Aclar/Al/PVC, PA/Al/PVC or Al/PVC/PVDC).

The light-sensitive active substance contained in ADEFIN XL is protected from light inside and outside its packaging. The tablets must be protected from humidity and must therefore only be removed from the foil immediately before use.

6.5 Nature and contents of container

ADEFIN XL 30 mg: Al/PVC/PVDC, Aclar/Al/PVC or PP/Al blister packs of 30 tablets.

ADEFIN XL 60 mg: PA/Al/PVC, Al/PVC/PVDC, Aclar/Al/PVC or PP/Al blister packs of 30 tablets.

Not all pack types may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

In ADEFIN XL, the medication is contained within a non-absorbable shell that slowly releases the medicine for the body to absorb. When this process is completed, the empty tablet is eliminated from the body and may be noticed in the stool.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

22 December 2005

10. Date of Revision of the Text

12 October 2018

Section	Summary of changes
-	Revised to SmPC format
4.5	Duplicate information re anti-hypertensive removed.
4.6	Information regarding animal studies and cross-reference to section 5.3