

# AUSTRALIAN PRODUCT INFORMATION

## ADEFIN XL30 ADEFIN XL 60



*Nifedipine modified release tablet*

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### 1 NAME OF THE MEDICINE

Nifedipine

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADEFIN XL tablets are a controlled release formulation (GITS, GastroIntestinal Therapeutic System) containing nifedipine USP 30 mg or 60 mg as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3 PHARMACEUTICAL FORM

Adefin XL 30 : Round, biconvex, rose-pink, film-coated tablet with "30" printed in black on one side, the tablet diameter being 9 mm.

Adefin XL 60 : Round, biconvex, rose-pink, film-coated tablet with "60" printed in black on one side, the tablet diameter being 11 mm.

ADEFIN XL tablets are similar in appearance to conventional tablets. Each tablet consists of a semipermeable membrane surrounding an osmotically active core. The core itself is divided into two layers: an "active" layer containing nifedipine, and a "push" layer containing pharmacologically inert but osmotically active components. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the nifedipine layer, releasing nifedipine through a precision laser-drilled tablet orifice in the "active" layer. The coating of ADEFIN XL remains intact during the gastrointestinal passage and is eliminated in the faeces.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

ADEFIN XL is indicated for:

1. the treatment of mild to moderate hypertension
2. the prophylaxis of chronic stable angina pectoris.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

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

As a rule, the tablets are swallowed whole **without chewing or being broken up** with a little liquid. They may be taken with or without food, however grapefruit juice is to be avoided.

*Hypertension.* In general, ADEFIN XL should be initiated with 30 mg once daily. A starting dose of 20 mg may be considered when medically indicated. Monitoring of trough blood pressure should be

done initially to ensure blood pressure control lasts over the dosing interval. Depending on the severity of the disease and the patient's response, the dose can be decreased to 20 mg or increased in stages to 120 mg daily. In general, titration should proceed over a 7 to 14 day period so that the physician 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 per day is not recommended.

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

*Chronic Stable Angina.* ADEFIN XL 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 per day in patients with angina is limited.

The initiation of ADEFIN XL therapy in South Asians who have not previously taken nifedipine should start at low doses (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Co-administration with CYP3A4 inhibitors or inducers may require nifedipine dose adjustment or for nifedipine not to be used at all (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

### 4.3 CONTRAINDICATIONS

ADEFIN XL is contraindicated in:

- patients with known hypersensitivity to nifedipine or related dihydropyridine calcium channel blockers or to any of the excipients
- female patients throughout pregnancy
- breastfeeding
- patients with cardiogenic shock
- patients with a Kock pouch (ileostomy after proctocolectomy)
- patients being administered rifampicin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
- patients within the first 8 days of an acute episode of myocardial infarction.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### **Excessive Hypotension**

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

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

#### **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, ADEFIN XL should be withdrawn if a causal relationship is suspected.

### **Beta Blocker Withdrawal**

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

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

### **Congestive Heart Failure**

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

### **Peripheral Oedema**

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

### **Hypotension/Heart Rate**

Because ADEFIN XL (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.

### **Acute Treatment of Angina Pectoris**

ADEFIN XL is not suitable for the acute treatment of angina pectoris due to delayed absorption of the medicine from the modified release dosage formulation.

### **Use in Diabetes**

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

### **Aortic Stenosis**

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

### **Severe Gastrointestinal Narrowing**

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

There have been rare reports of bowel obstruction requiring surgery in patients with known oesophageal stricture, small bowel stenosis, and after gastroplexy, due to the non-deformable nature of ADEFIN XL.

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

### **Shortened Transit Times**

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

### **Other Nifedipine Formulations**

ADEFIN XL tablets are not bioequivalent to immediate release nifedipine capsules and tablets, and patients should be carefully monitored if it is decided to switch between immediate release and modified release nifedipine or vice versa. ADEFIN XL may not be bioequivalent to modified-release nifedipine preparations available overseas.

### **Use in Hepatic Impairment**

#### ***Use in Patients with Liver Impairment***

ADEFIN XL should be used with caution in patients with mild, moderate or severe impaired liver function (see Section 5 PHARMACOLOGICAL PROPERTIES). A dose reduction may be required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Close monitoring of response and metabolic effect should apply. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment. Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

### **Use in the Elderly**

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

### **Paediatric Use**

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

### **Effects on Laboratory Tests**

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

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. 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.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### **Effects of other drugs on nifedipine**

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

Drugs, which are inhibitors of CYP3A4 and therefore may lead to increased plasma concentrations of nifedipine, such as:

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

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

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

#### ***Rifampicin***

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

**Upon co-administration of the following weak to moderate inhibitors of CYP3A4 the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered** (see Section 4.3 DOSE AND METHOD OF ADMINISTRATION).

#### ***Macrolide antibiotics (e.g. erythromycin)***

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

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

#### ***Anti-HIV Protease Inhibitors***

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

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

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

***Fluoxetine***

A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* the CYP3A4 mediated metabolism of nifedipine. Therefore, an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

***Nefazodone***

A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit CYP3A4 mediated metabolism of other medicines. Therefore, an increase of nifedipine plasma concentrations upon co-administration of both medicines cannot be excluded.

***Quinupristin/Dalfopristin***

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

***Valproic acid***

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

***Cimetidine***

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

***Diltiazem***

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

**Further studies*****Cisapride***

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

***CYP3A4-inducing anti-epileptic drugs such as phenytoin, carbamazepine and phenobarbital (phenobarbitone)***

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

## Effects of nifedipine on other drugs

### *Blood pressure lowering drugs*

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

- diuretics
- $\beta$ -blockers
- ACE-inhibitors
- angiotensin I (ATI) receptor – antagonists
- other calcium antagonists
- $\alpha$ -adrenergic blocking agents
- PDE5 inhibitors
- $\alpha$ -methyldopa

When nifedipine is used in conjunction with  $\beta$ -receptor blockers, patients should be carefully monitored since deterioration of heart failure is also known to develop in isolated cases.

### *Digoxin*

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

### *Quinidine*

Quinidine levels have been observed to decrease upon introduction of nifedipine and increase upon its withdrawal. For this reason, it is recommended that when nifedipine is either added to quinidine therapy or withdrawn from it, quinidine concentrations are monitored, and the dose adjusted accordingly. Some authors reported increased plasma levels of nifedipine upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of nifedipine. Therefore, if quinidine is added to existing nifedipine therapy, blood pressure should be monitored, and if necessary the dose of nifedipine should be reduced.

### *Tacrolimus*

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

### *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.

### **Interactions shown not to exist**

In drug interaction studies, aspirin, omeprazole, pantoprazole and ranitidine did not have clinically significant effects on the pharmacokinetics of nifedipine. Nifedipine did not have a clinically significant effect on the effect of 100 mg aspirin on platelet aggregation and bleeding time.

***Candesartan cilexetil, Irbesartan, Doxazosin.***

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

**Drug-food interactions*****Grapefruit***

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

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

**Other forms of interactions*****Barium Contrast X-Ray***

ADEFIN XL may cause false positive findings (eg. filling defects interpreted as polyp) 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 HPLC is unaffected.

**4.6 FERTILITY, PREGNANCY AND LACTATION****Effects on Fertility**

In isolated cases of *in vitro* fertilisation, calcium channel blockers like nifedipine have been associated with reversible biochemical changes in the head section of the spermatozoa that may result in impaired sperm function. In 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 possible causes.

**Use in Pregnancy**

Pregnancy Category: C

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

Nifedipine is contraindicated throughout pregnancy. Medicines in this class carry the potential to produce foetal hypoxia, caesarean deliveries, prematurity and intrauterine growth retardation, which may be associated with maternal hypotension. Nifedipine was shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies are possibly a result of compromised uterine blood flow. Nifedipine administration has been associated with a variety of embryotoxic, placentotoxic and 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 and

several times the recommended maximum dose for humans. There are no adequate and well controlled studies in pregnant women.

### Use in Lactation

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

## 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. This applies particularly at the start of treatment, on changing doses, and in combination with alcohol.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Drug Reactions (ADRs) listed under “common” were observed with a frequency below 3 % with the exception of oedema (9.9 %) and headache (3.9 %). ADR is defined as a response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial database: nifedipine n = 6,486; placebo n = 5,326) are listed below.

The frequencies are defined as:

Common  $\geq 1/100$  to  $< 1/10$

Uncommon  $\geq 1/1000$  to  $< 1/100$

Rare  $\geq 1/10000$  to  $< 1/1000$

**Table 1. ADRs reported based on clinical trial data**

System Organ Class	Common	Uncommon	Rare
<b>Immune system disorders</b>		Allergic reaction Allergic oedema/angioedema (including larynx oedema*)	Urticaria
<b>Psychiatric disorders</b>		Anxiety reactions Sleep disorders	
<b>Nervous system disorders</b>	Headache Dizziness	Paraesthesia Somnolence Tremor Vertigo Migraine	Hypaesthesia Dysaesthesia
<b>Eye disorders</b>		Visual disturbances	
<b>Cardiac disorders</b>	Palpitation	Chest pain Angina pectoris Tachycardia	Chest pain substernal Cardiovascular disorder
<b>Vascular disorders</b>	Oedema Vasodilatation	Syncope Hypotension	
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea Nosebleed Nasal congestion	
<b>Gastrointestinal disorders</b>	Constipation	Gastrointestinal and abdominal pain	Gingival hyperplasia Anorexia

		Nausea Dry mouth Dyspepsia Vomiting Flatulence Diarrhoea	Eructation Gastrointestinal disorder GGT increased Gingivitis
<b>Hepatobiliary disorders</b>		Increase in transaminases	
<b>Skin and cutaneous tissue disorders</b>		Pruritus Rash Erythema	Sweating Macupapular rash Pustular rash Vesiculobullous rash
<b>Musculoskeletal and connective tissue disorders</b>		Muscle cramps Joint swelling Leg cramps	Arthralgia Myalgia Joint disorder
<b>Renal and urinary disorders</b>		Polyuria Dysuria	Urinary frequency increased
<b>General disorders and administration site conditions</b>	Feeling unwell Asthenia	Unspecific pain Chills Leg pain	Fever
<b>Reproductive system and breast disorders</b>		Erectile dysfunction	
* 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% (30 mg) to 30% at the highest dose studied (180 mg). In clinical trials of 20 mg the frequency of peripheral oedema ranged from 0% to 4%.

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

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

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

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

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

In a double-blind comparison of ADEFIN XL and ADEFIN tablets, the incidence of vasodilator reactions did not differ.

### Post marketing experience

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

**Table 2. ADRs reported based on post-marketing experience**

System Organ Class (MedDRA)	Not known
<b>Blood and lymphatic system disorders</b>	Agranulocytosis Leukopenia
<b>Immune system disorders</b>	Anaphylactic/anaphylatoid reactions
<b>Metabolism and nutrition disorders</b>	Hyperglycaemia
<b>Nervous system disorders</b>	Hypoaesthesia Somnolence
<b>Eye disorders</b>	Eye pain Blurred vision
<b>Cardiac disorders</b>	Chest pain (angina pectoris)
<b>Respiratory, thoracic, and mediastinal disorders</b>	Dyspnoea
<b>Gastrointestinal disorders</b>	Vomiting Gastro-oesophageal sphincter insufficiency Gum hyperplasia Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Oesophagitis Gum disorder
<b>Hepatobiliary disorders</b>	Jaundice
<b>Skin and subcutaneous tissue disorders</b>	Toxic Epidermal Necrolysis (exfoliative dermatitis) Erythromelalgia Photosensitivity allergic reaction Palpable purpura Gynaecomastia
<b>Musculoskeletal and connective tissue disorders</b>	Arthralgia Myalgia Muscle cramps
<b>Investigations</b>	Weight loss ALT increased

### Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

### Symptoms

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

### Management of Overdose

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

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

Haemodialysis is ineffective in removing nifedipine in the body because nifedipine is not dialysable (high plasma protein binding, relatively low volume of distribution), but plasmapheresis may be considered.

Bradycardiac 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 administered slowly intravenously and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If the effects are inadequate, the treatment can be continued with ECG monitoring, with the addition of a beta-sympathomimetic medicine (eg. isoprenaline 0.2 mg slowly intravenously, repeated if necessary as a continuous infusion at 5 microgram/min). If this is still insufficient to return the blood pressure to normal, vasoconstricting sympathomimetics such as dopamine or norepinephrine (noradrenaline) may be 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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### **Mechanism of Action**

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

#### ***Hypertension***

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

### **Clinical Trials**

The pivotal clinical studies were performed in patients with chronic stable angina. In these studies, ADEFIN XL at doses of 30 mg and 60 mg once daily improved exercise tolerance test (ETT) parameters in reference to baseline. ADEFIN XL 30 mg daily showed small but sub-optimal benefit. When titrated to the dose of 60 mg once daily, ADEFIN XL was as effective as atenolol 100 mg once daily. In patients already on beta-blocker therapy, ADEFIN XL improved ETT parameters and time to 1 mm ST depression, and at doses of up to 90 mg once daily, ADEFIN XL was more effective than modified release nitrates (isosorbide mononitrate 50 mg once daily, isosorbide dinitrate 20 to 40 mg twice daily). However in this particular study, ETT performance was measured at 22 to 24 hours after the last dose of ADEFIN XL and isosorbide mononitrate, and about 15 hours after last dose of isosorbide dinitrate. Therefore, the higher efficacy observed for ADEFIN XL may be attributable to the difference in pharmacokinetics between ADEFIN XL and nitrates. In pivotal and supportive clinical studies, the duration of treatment with ADEFIN XL was limited to 2 to 12 weeks only, and the majority of patients in these studies were already on background beta-blocker therapy. Data in patients with unstable angina, asymptomatic ischaemia, vasospastic angina and post-myocardial infarction are limited. Data on monotherapy with ADEFIN XL are limited and based on trials of short duration ( $\leq 4$  weeks).

## **5.2 PHARMACOKINETIC PROPERTIES**

### **Absorption and distribution**

Nifedipine is almost completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero-order absorption kinetics after ADEFIN XL administration and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24 hour dosing interval. At steady state, the bioavailability of ADEFIN XL is 86% relative to an immediate release dosage form which has a systemic availability of 45 to 68%. Administration of ADEFIN XL 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 (ie. short bowel syndrome) may, however, influence the pharmacokinetic profile of the medicine, which could result in lower plasma concentrations. Pharmacokinetics of ADEFIN XL 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 either in the presence or absence of food.

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

### **Metabolism and excretion**

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

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

Nifedipine is excreted in the form of its metabolites predominantly via the kidneys (60 to 80%) 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.

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 (eg. Mexican, Japanese and South Asians). Currently, confirmatory studies only exist for the South Asian population. In comparison to Caucasians, there were increases in AUC 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 by approximately two-fold. Although haemodynamic responses in the South Asian healthy volunteers were similar to those reported in Caucasians, lower doses of nifedipine may be required in South Asian patients at the beginning of ADEFIN XL therapy.

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

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

#### Carcinogenicity

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Besides the active ingredient, ADEFIN XL 30 mg and 60 mg tablets also contain the following inactive ingredients: polyethylene oxide, magnesium stearate, sodium chloride, hypromellose, iron oxide red (CI 77491), cellulose acetate, macrogol 3350, OPACODE monogramming ink S-1-17823 Black (ID 12108) and OPADRY LY-S-24914 (ID 2928).

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

- Adefin XL 30** : Store below 30°C. Protect from light.
- Adefin XL 60** : Blister packs (PP/Al) – Store below 25°C. Protect from light.  
 Blister packs (PVC/PVDC/Al) - Store below 25°C.  
 Blister packs (PA/Al/PVC/Al) – Store below 30°C.  
 Blister packs (PVC/PE/PCTFE (Aclar)/Al) - Store below 30°C.

The drug release mechanism of ADEFIN XL is triggered by moisture. Contact of the tablets with moisture may not be apparent but loss of contents may have already occurred. To prevent this, the tablet must be kept in its original blister-foil packaging until immediately before use.

## 6.5 NATURE AND CONTENTS OF CONTAINER

- Adefin XL 30 : Packed in Al/Al blister packs supplied in packs of 10\* or 30 tablets.
- Adefin XL 60 : Packed in blister packs supplied in packs of 30 tablets.  
 Blister packs (PP/Al)\*  
 Blister packs (PA/Al/PVC/Al)  
 Blister packs (PVC/PVDC/Al)\*  
 Blister packs (PVC/PE/PCTFE (Aclar)/Al)\*

\*Some strengths, pack sizes and/or pack types may not be marketed.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

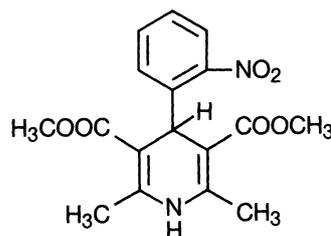
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical Structure

Chemical name: Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-3,5-pyridinedicarboxylate

Structural formula:



Molecular formula:  $C_{17}H_{18}N_2O_6$

Molecular Weight: 346.3

**CAS Number**

21829-25-4

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

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

S4 (Prescription Only Medicine)

**8 SPONSOR****Alphapharm Pty Limited**

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**9 DATE OF FIRST APPROVAL**

14/11/2002

**10 DATE OF REVISION**

03 January 2020

**Summary Table of Changes**

<b>Section Changed</b>	<b>Summary of New Information</b>
<b>All</b>	Reformat of the PI to align with updated Australian form for providing product information Minor editorial changes
<b>4.6</b>	Pregnancy category definition added for clarity

Adefin XL\_pi\Nov19/01