



21 August 2020

Dear Healthcare Professional

**RE: Adalat OROS®**

Thank you for your request for information regarding Adalat OROS (nifedipine). Your enquiry was passed to the Medical Department by our representative, Sharon Burns.

Please find the relevant information attached. Note that Bayer Australia Limited does not endorse the usage of its products in any indication, dose, duration or manner that is inconsistent with the approved labelling. All opinions and views are of the respective authors and do not represent a recommendation or endorsement by Bayer Australia Limited.

We trust you will find this information useful. Should you require any further assistance, please do not hesitate to contact us again.

Yours Sincerely

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## ADALAT OROS AND SAFETY UPON CRUSHING

The *Description* section of the Adalat OROS Product Information<sup>1</sup> states:

*Adalat OROS tablets are a controlled release formulation (GITS, GastroIntestinal Therapeutic System) containing nifedipine 20 mg, 30 mg or 60 mg.*

*Adalat OROS 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 Adalat OROS remains intact during the gastrointestinal passage and is eliminated in the faeces.*

The *Pharmacokinetics* section of the Adalat OROS Product Information<sup>1</sup> states:

*Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero-order absorption kinetics after Adalat OROS 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.*

The *Dosage and Administration* section of the Adalat OROS Product Information<sup>1</sup> states:

*The tablets are swallowed whole without chewing or being broken up with a little liquid.*

Please consult the enclosed Adalat OROS Product Information<sup>1</sup> for further details.

It should be noted that the crushing of Adalat OROS before administration is outside of the approved Australian product label. Bayer only recommends the use of Adalat OROS in accordance with the Australian Product Information. The use of Adalat OROS outside of the approved Australian product label is at the clinical discretion and responsibility of the healthcare professional.

Dividing or crushing Adalat XL\* tablet would damage the release mechanism and result in a large immediate release of the drug<sup>2</sup> therefore it is not recommended.

No studies have been conducted to investigate the safety, efficacy or pharmacokinetics or *in vitro* release of crushed Adalat OROS tablets.

\* Please note: Adalat XL is not a product marketed in Australia.

An extensive search of the clinical literature identified the below summarised case reports which reported on the safety of using crushed nifedipine extended release tablets.

Schier, J.G. *et al.* (2003)<sup>3</sup> reported a case in which a crushed extended-release (XL) nifedipine tablet contributed to a patient fatality. A 38-year-old woman with multiple medical problems presented to the hospital in acute respiratory distress and was diagnosed with acute pulmonary oedema and pneumonia. After initial stabilisation, her medications were changed to oral hydralazine, labetalol, and nifedipine XL. These medications were crushed and administered through a nasogastric tube. The patient developed worsening bradycardia with hypotension and experienced a systolic cardiac arrest. She was resuscitated; however, the following morning, another dose of labetalol and nifedipine XL was crushed and administered through the nasogastric tube. She again developed worsening bradycardia with hypotension and ultimately died.

The author noted that *“the administration of a crushed nifedipine XL tablet resulted in the patient's severe hypotension. The concurrent administration of labetalol prevented a compensatory heart rate increase. The repeated administration of nifedipine XL in the same manner underscores a fundamental problem in healthcare worker communication and drug delivery system comprehension. Use of the Naranjo probability scale indicated a highly probable relationship between the patient's hypotension and the nifedipine and labetalol therapy. Simultaneous administration of a beta-blocker and a calcium-channel blocker may produce synergistic effects. The release characteristics of oral controlled-release medications are destroyed when crushed, resulting in the rapid bioavailability of the total drug amount. The importance of education and communication among nurses, physicians, and pharmacists regarding the mechanism of action of controlled-release medications and their administration needs to be emphasized.”*

Bassett, R.A. *et al.* (2014)<sup>4</sup> reported a case of severe calcium channel blocker (CCB) toxicity following enteral administration of a single crushed tablet of extended-release (non-brand specified) nifedipine. A 69-year-old man who had stabilised after treatment for gastrointestinal (GI) bleeding was transitioned to his home medication regimen on hospital day 5. The patient's nurse crushed his nifedipine extended-release 90mg pill and administered it through the patient's nasal duodenal tube. One hour after exposure his physical examination was significant for: blood pressure 65/44 mmHg, pulse 80 beats/minute in a ventricularly paced rhythm, and a decreased level of consciousness. Over the next 24 hours the patient was treated with crystalloid fluid, glucagon, calcium and titrated infusions of epinephrine, norepinephrine, phenylephrine, and dopamine. He did not have evidence of a recurrence of his GI bleed or other explanation for his hypotension. Twenty-four hours after exposure, the patient's blood pressure returned back to the normal range without vasopressor support. The author noted that *“although calcium channel blocker toxicity is not unusual, severe poisoning following exposure to a single crushed tablet of extended-release formulation is rarely reported in the literature. The toxicokinetics of a crushed extended-release formulation of nifedipine are not well-described. In this case, the patient required hemodynamic support for 24 hours. CCB poisoning in any manner can be life threatening but can be especially dangerous in cases of extended release mechanism-defeat. There is potential to absorb massive amounts of concentrated drug; additionally, if the error is not identified immediately, it may go unrecognized or inappropriately treated. Although efforts to reduce medication errors have resulted in “do not crush” lists and “do not crush” labels, this case illustrates that the potential still exists for this type of medication error to occur. Increased awareness and communication among physicians, nurses, and pharmacy staff is important to help mitigate the risks associated with extended release formulations.”*

We have referenced below the abovementioned clinical papers. If you would like a copy of any of the references listed below please contact the Bayer Medical Information Department via email at [medinfo.anz@bayer.com](mailto:medinfo.anz@bayer.com).

## REFERENCES

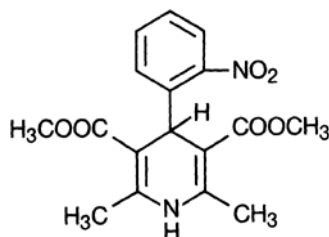
1. Adalat OROS Product Information. Date of most recent amendment: 03 May 2016.
2. Adalat XL Canadian Product Monograph. Date of revision: 25 July 2016
3. Schier, J.G. *et al.* (2003) Fatality from administration of labetalol and crushed extended-release nifedipine. *Ann Pharmacother.* Oct;37(10):1420-3.
4. Bassett, R.A. *et al.* (2014) Crushing medication error: Calcium channel blocker toxicity following administration of a crushed extended-release tablet of nifedipine. *Clinical Toxicology.* 52(7): 803. Meeting Abstract.

# ADALAT® OROS

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Nifedipine is dimethyl 1,4-dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-3,5-pyridinedicarboxylate, C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>, MW 346.3, CAS Registry No. [21829-25-4]. Its structural formula is shown below.



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

### DESCRIPTION

Adalat OROS tablets are a controlled release formulation (GITS, GastroIntestinal Therapeutic System) containing nifedipine 20 mg, 30 mg or 60 mg. Besides the active ingredient, Adalat OROS 20 mg, 30 mg and 60 mg tablets also contain the following inactive ingredients: polyethylene oxide, magnesium stearate, sodium chloride, hypromellose, iron oxide red (CI 77491), hydroxypropylcellulose, cellulose acetate, macrogol 3350, titanium dioxide and propylene glycol.

Adalat OROS 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 Adalat OROS remains intact during the gastrointestinal passage and is eliminated in the faeces.

All strengths of Adalat OROS are round, biconvex shaped, rose-pink, film-coated tablets. Tablet diameters are 8.4 mm (20 mg), 9 mm (30 mg) and 11 mm (60 mg). Adalat OROS 20 mg tablets are marked in black with the product name on one side ("Adalat 20") and the Adalat OROS 30 mg and 60 mg tablets are marked with the dose strength on one side ("30" or "60").

### PHARMACOLOGY

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 in Angina**

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

## Pharmacokinetics

Nifedipine is almost completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero-order absorption kinetics after Adalat OROS 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 Adalat OROS is 86% relative to an immediate release dosage form which has a systemic availability of 45 – 68%. Administration of Adalat OROS in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced gastrointestinal retention times over prolonged periods (i.e., short bowel syndrome) may, however, influence the pharmacokinetic profile of the medicine, which could result in lower plasma concentrations. Pharmacokinetics of Adalat OROS 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).

The active substance nifedipine is almost completely metabolised in the liver, primarily by oxidative processes: cytochrome P450 3A4 (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 – 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 P-450(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 Adalat OROS therapy.

## INDICATIONS

Adalat OROS is indicated for:

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

## **CONTRAINDICATIONS**

Adalat OROS 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
- breast feeding
- patients with cardiogenic shock
- patients with a Kock pouch (ileostomy after proctocolectomy)
- patients being administered rifampicin (see Interaction with Other Medicines)
- patients within the first 8 days of an acute episode of myocardial infarction

## **PRECAUTIONS**

### **Excessive Hypotension**

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

Adalat OROS 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, Adalat OROS 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.

Adalat OROS 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 Adalat OROS 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 Adalat OROS (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**

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

### **Aortic Stenosis**

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

### **Severe Gastrointestinal Narrowing**

As with any other non-deformable material, caution should be used when administering Adalat OROS 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 Adalat OROS. In single cases obstructive symptoms have been described without known history of gastrointestinal disorders.

### **Shortened Transit Times**

The sustained release of Adalat OROS may be impaired in chronic diarrhoea (e.g., Crohn's disease, ulcerative colitis) or short bowel syndrome, when the gastrointestinal transit time is less than 18 – 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 Adalat tablets taken twice daily should be used.

### **Other Nifedipine Formulations**

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

### **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**

Category C: Nifedipine is contraindicated throughout pregnancy. Medicines in this class carry the potential to produce fetal hypoxia, caesarean deliveries, prematurity and intrauterine growth retardation, which may be associated with maternal hypotension. Nifedipine 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 fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or fetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans. There are no adequate and well controlled studies in pregnant women.

### **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.

### **Paediatric use**

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

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

ADALAT OROS should be used with caution in patients with mild, moderate or severe impaired liver function (see PHARMACOLOGY). A dose reduction may be required (see DOSAGE AND 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 Adalat OROS 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.

### **Use in Diabetes**

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

### **Carcinogenicity/Mutagenicity**

Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. *In vitro* and *in vivo* mutagenicity studies were negative.

## INTERACTION WITH OTHER MEDICINES

Nifedipine is metabolised via CYP3A4, 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, 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 drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

### ***Drugs that affect nifedipine***

Nifedipine is metabolised via CYP3A4, 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.

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 nifedipine in combination with rifampicin is therefore 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 DOSAGE AND 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 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 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 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 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,
- $\alpha$ -methyl dopa.

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.

#### **Drug-food interactions**

##### *Grapefruit*

Grapefruit juice inhibits CYP3A4. 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.

#### **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.

#### **Other Forms of Interactions**

##### *Barium Contrast X-Ray*

Adalat OROS may cause false positive findings (e.g. 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.

#### **Effect 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.

#### **Effect on Laboratory Tests**

Rare, usually transient, but occasionally significant elevations of enzymes such as 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.

## ADVERSE 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     ≥ 1/100 to < 1/10  
 Uncommon   ≥ 1/1000 to < 1/100  
 Rare         ≥ 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>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>
<b>Gastrointestinal disorders</b>	Constipation	Gastrointestinal and abdominal pain Nausea Dry mouth Dyspepsia Vomiting Flatulence Diarrhoea	Gingival hyperplasia Anorexia 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% on 30 mg to 30% at the highest dose studied (180 mg). In clinical trials of 20 mg the frequency of peripheral oedema ranged from 0% to 4%.

There have been a small number of reports of chest pain not associated with myocardial infarction occurring soon after administration of a single dose. 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 AP 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 Adalat OROS and Adalat 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
Blood and lymphatic system disorders	Agranulocytosis Leukopenia
Immune system disorders	Anaphylactic/ anaphylactoid reactions
Metabolism and nutrition disorders	Hyperglycaemia
Nervous system disorders	Hypoaesthesia Somnolence
Eye disorders	Eye pain Blurred vision
Cardiac disorders	Chest pain (Angina pectoris)
Respiratory, thoracic, and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Vomiting Gastro-oesophageal sphincter insufficiency Gum hyperplasia Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Oesophagitis Gum disorder
Hepatobiliary disorders	Jaundice



System Organ Class (MedDRA)	Not known
Skin and subcutaneous tissue disorders	Toxic Epidermal Necrolysis (exfoliative dermatitis) Erythromelalgia Photosensitivity allergic reaction Palpable purpura Gynaecomastia
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Muscle cramps
Investigations	Weight loss ALT increased

## DOSAGE AND ADMINISTRATION

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

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

**Hypertension** - In general Adalat OROS therapy 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 – 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.

**Chronic Stable Angina** - Adalat OROS 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 Adalat OROS therapy in South Asians who have not previously taken nifedipine should start at low doses (see PHARMACOKINETICS).

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

## OVERDOSAGE

### 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 Adalat OROS. 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 – 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 µg/min). If this is still insufficient to return the blood pressure to normal, vasoconstricting sympathomimetics such as dopamine or noradrenaline may be additionally administered. The dosage of these 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.

### **PRESENTATION AND STORAGE CONDITIONS**

Adalat OROS tablets are round, biconvex, rose-pink, film-coated tablets, supplied in packs of 10 or 30 tablets. Adalat OROS 20 mg tablets are marked in black with the product name on one side ("Adalat 20") and the Adalat OROS 30 mg and 60 mg tablets are marked with the dose strength on one side ("30" or "60").

Not all pack sizes may be marketed.

The drug release mechanism of Adalat OROS 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.

#### ***Container types and Storage Conditions for Adalat Oros 20 mg:***

Blister Pack (PA/Al/PVC/Al) – Store below 30 °C.

Blister Pack (PVC/PVDC/Al) – Store below 30 °C.

**Container types and Storage Conditions for Adalat Oros 30 mg:**

Blister Pack (PA/Al/PVC/Al) – Store below 30 °C.

Blister Pack (PVC/PE/PCTFE/Al) – Store below 30 °C

Blister Pack (PVC/PVDC/Al) – Store below 25 °C.

**Container types and Storage Conditions for Adalat Oros 60 mg:**

Blister Pack (PA/Al/PVC/Al) – Store below 30 °C.

Blister Pack (PVC/PVDC/Al) – Store below 25 °C.

Blister Pack (PP/Al) – Store below 25 °C. Protect from light.

Blister Pack (PVC/PE/PCTFE/Al) – Store below 30 °C.

Not all packaging material types may be marketed. Refer to medicine carton for storage instructions.

**NAME AND ADDRESS OF THE SPONSOR**

BAYER AUSTRALIA LTD  
ABN 22 000 138 714  
875 Pacific Highway  
PYMBLE NSW 2073

**POISON SCHEDULE OF THE MEDICINE**

PRESCRIPTION ONLY MEDICINE

**DATE OF FIRST INCLUSION IN THE ARTG:** 23 July 1997

**DATE OF MOST RECENT AMENDMENT:** 3 May 2016

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