

## PRODUCT MONOGRAPH

**Pr ADALAT<sup>®</sup> XL<sup>®</sup>**

Nifedipine extended-release tablets Bayer Standard

**20 mg, 30 mg and 60 mg nifedipine**

**Antianginal/Antihypertensive Agent**

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20 mg, 30 mg and 60 mg nifedipine

## **THERAPEUTIC CLASSIFICATION**

Antianginal/Antihypertensive Agent

## **SYSTEM COMPONENTS AND PERFORMANCE**

ADALAT XL (nifedipine) extended release tablets, while similar in appearance to a conventional tablet, nonetheless consists of a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers: an "active" layer containing the drug, 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 drug layer, forcing drug through the orifice in the active layer.

Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero as drug is exhausted from the tablet. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

## **ACTION AND CLINICAL PHARMACOLOGY**

ADALAT XL (nifedipine) is a calcium ion influx inhibitor (calcium channel blocker or calcium ion antagonist).

The antianginal and antihypertensive actions of nifedipine are believed to be related to a specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Nifedipine selectively inhibits the transmembrane influx of calcium through the slow channel without affecting, to any significant degree, the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within the muscle cells and an inhibition of the contractile processes. Nifedipine does not alter 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.

Nifedipine dilates the main coronary arteries and coronary arterioles both in normal and ischemic regions resulting in an increase in blood flow and hence in myocardial oxygen delivery.

Nifedipine by its vasodilatory action on peripheral arterioles, reduces the total peripheral vascular resistance. This reduces the workload of the heart and thus reduces myocardial energy consumption and oxygen requirements which probably accounts for the effectiveness of nifedipine in chronic stable angina.

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and subsequent reduction in peripheral vascular resistance. The increased peripheral vascular 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 active tension reflects an increase in cytosolic free calcium.

The negative inotropic effect of nifedipine is usually not of major clinical significance because at therapeutic doses, nifedipine's vasodilatory property evokes a baroreceptor mediated reflex tachycardia which tends to counterbalance this negative inotropic effect. Continued administration of nifedipine to hypertensive patients has shown no significant increase in heart rate.

Although nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

The International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment trial called INSIGHT was a prospective double-blind trial with dynamic randomisation which enrolled mainly white hypertensive men and women. The primary endpoint was a composite of death from any cardiovascular or cerebrovascular cause, together with non-fatal stroke, myocardial infarction, and heart failure. The secondary endpoint included total mortality, death from a vascular cause, and non-fatal vascular events including transient ischemic attacks, angina (new or worsening) and renal failure. INSIGHT was designed to establish the superiority of ADALAT XL over the diuretic combination co-amilozide (hydrochlorothiazide and amiloride). When the results of the Swedish Trial in Old Patients with Hypertension-2 study (STOP-2) became known and because these results suggested that calcium-channel blockade and diuretic treatment had similar efficacy in preventing complications, but before the patient code in INSIGHT was broken, a secondary, non-inferiority analysis was added.

INSIGHT randomized 6575 mild to moderate essential hypertensive or isolated systolic hypertensive patients, 55 – 80 years of age, with at least one other cardiovascular risk factor to nifedipine and co-amilozide. Patients were excluded if they had heart failure with low ejection fraction (< 40%), unstable angina, PTCA (Percutaneous Transluminal Coronary Angioplasty) or CABG (Coronary Artery Bypass Grafting) within 6 months prior to study start, or myocardial infarction or stroke in the 12 months prior to study start. Doses of each drug were titrated to

achieve a target blood pressure of 140/90 mmHg (or drop of 20/10 mmHg) and if that target was not reached additional drugs could be added (atenolol and subsequently enalapril). On average patients were treated for 3.5 years. After placebo washout, the baseline blood pressure was 173/99 mmHg and decreased to 138/82 mmHg by the end of the trial in both groups. Heart rate was not different between the groups. At the end of the study 69 and 72% of patients on ADALAT XL and hydrochlorothiazide/amiloride, respectively, were on monotherapy. All endpoints were assessed and adjudicated by the Critical Events Committee. The overall results of the study in the table just below show that ADALAT XL was not inferior to the diuretic combination co-amilozide:

	<b>ADALAT XL</b>	<b>Hydrochlorothiazide/ Amiloride</b>	<b>Odds Ratio (95% CI)</b>	<b>p-value</b>
Primary Outcomes Composite	200 (6.3%)	182 (5.8%)	1.11 (0.90-1.36)	0.34
Secondary Outcomes Composite	383 (12.1%)	397 (12.5%)	0.96 (0.83-1.12)	0.62
Total Mortality	153 (4.8%)	152 (4.8%)	1.01 (0.80-1.27)	0.95
All Adverse Events	1546 (49%)	1327 (42%)	N/A	< 0.001
Serious Adverse Events	796 (25%)	880 (28%)	N/A	0.02

### **Pharmacokinetics**

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero-order absorption kinetics after ADALAT XL (nifedipine) 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. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate release ADALAT capsule at t.i.d. dosing than with once daily ADALAT XL tablets. At steady-state the bioavailability of the ADALAT XL tablet is 86% relative to ADALAT capsules. Administration of the ADALAT XL tablet in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (i.e., short bowel syndrome), however, may influence the

pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations. Pharmacokinetics of ADALAT XL tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food. The bioavailability of the 20 mg tablet is directly proportional to the 30 mg tablet.

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. The main metabolite (95%) is the hydroxycarboxylic acid derivative, the remaining 5% is the corresponding lactone. Only traces (less than 0.1% of the dose) of unchanged nifedipine can be detected in the urine. Thus, the pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in hemodialysis or CAPD (continuous ambulatory peritoneal dialysis) have not reported significantly altered pharmacokinetics of nifedipine.

Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Pharmacokinetic studies in patients with hepatic cirrhosis showed a clinically significant prolongation of elimination half-life and a decrease in total clearance of nifedipine. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment (see **PRECAUTIONS**).

Nifedipine is metabolized by the cytochrome P450 enzyme system, predominantly via CYP3A4, but also by CYP1A2 and CYP2A6 isoenzymes.

Compounds found in grapefruit juice inhibit the cytochrome P450 system, especially CYP3A4. In a grapefruit juice-nifedipine interaction study in healthy male volunteers, pharmacokinetics of nifedipine showed significant alteration. Following administration of a single dose of nifedipine 10 mg with 250 mL grapefruit juice, the mean value of nifedipine AUC increased by 34% and the T<sub>max</sub> increased from 0.8 hours to 1.2 hours as compared to water (see PRECAUTIONS - Interaction with Grapefruit Juice).

## **INDICATIONS AND CLINICAL USE**

### **Chronic Stable Angina**

ADALAT *XL* (nifedipine) is indicated in the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates, or who cannot tolerate these agents.

ADALAT *XL* may be used in combination with beta blocking drugs in patients with chronic stable angina. However, available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely, since severe hypotension can occur from the combined effects of the drugs (see **WARNINGS**).

### **Hypertension**

ADALAT *XL* is indicated in the management of mild to moderate essential hypertension.

ADALAT *XL* should normally be used in those patients in whom treatment with diuretics or beta blocker has been ineffective, or has been associated with unacceptable adverse effects.

ADALAT *XL* can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of ADALAT *XL* with a diuretic has been found compatible and has shown added antihypertensive effect. Concurrent administration of low doses of ADALAT *XL* and enalapril has been shown to produce an enhanced antihypertensive effect with no additional safety concerns when compared to that observed with either of the monotherapies.

Safety of concurrent use of ADALAT *XL* with other antihypertensive agents has not been established.

## **CONTRAINDICATIONS**

ADALAT XL (nifedipine) is contraindicated in pregnancy, during lactation, and in women of childbearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals.

An increase in the number of fetal mortalities and resorptions occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice, rats, and rabbits. Fetal malformations occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice and 100 mg/kg to pregnant rats.

In patients with hypersensitivity to ADALAT.

In patients with severe hypotension or cardiovascular shock.

Nifedipine must not be used in combination with rifampicin because insufficient plasma levels of nifedipine may result due to enzyme induction.

## **WARNINGS**

### **Excessive Hypotension in Patients with Angina**

Since ADALAT XL (nifedipine) lowers peripheral vascular resistance and blood pressure, ADALAT XL should be used cautiously in patients with angina who are prone to develop hypotension and those with a history of cerebrovascular insufficiency. Occasional patients have had excessive and poorly tolerated hypotension. Syncope has been reported (see ADVERSE REACTIONS). These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers. If excessive hypotension occurs, dosage should be lowered or the drug should be discontinued (see [CONTRAINDICATIONS](#)).

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine, with a beta blocker, who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the

combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours), should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina.

### **Increased Angina and/or Myocardial Infarction**

Rarely, patients, particularly those who have severe obstructive coronary artery disease have developed well-documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of the response is not established.

Since there has not been a study of ADALAT *XL* in acute myocardial infarction reported, similar effects of ADALAT *XL* to that of immediate-release nifedipine cannot be excluded. Immediate-release nifedipine is contraindicated in acute myocardial infarction.

### **Beta Blocker Withdrawal**

Patients with angina recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of treatment with ADALAT *XL* will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and initiation of nifedipine. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning ADALAT *XL*.

### **Patients with Heart Failure**

There have been isolated reports of severe hypotension and lowering of cardiac output following administration of nifedipine to patients with severe heart failure. Thus, ADALAT *XL* should be used cautiously in patients with severe heart failure. Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine therapy.

In patients with severe aortic stenosis, nifedipine will not produce its usual afterload reducing effects and there is a possibility that an unopposed negative inotropic action of the drug may produce heart failure if the end-diastolic pressure is raised. Caution should therefore be exercised when using ADALAT *XL* in patients with these conditions.

### **Patients with Pre-Existing Gastrointestinal Narrowing**

Since the ADALAT *XL* delivery system contains a non-deformable material, caution should be used when administering ADALAT *XL* in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of ADALAT *XL* tablets. In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders. Bezoars can occur in very rare cases and may require surgical intervention. ADALAT *XL* must not be used in patients with a Kock pouch (ileostomy after proctocolectomy).

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

## **PRECAUTIONS**

### **Hypotension/Heart Rate**

Because ADALAT *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 (see **WARNINGS**).

### **Peripheral Edema**

Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, has been reported to occur in patients treated with ADALAT *XL* (see **ADVERSE REACTIONS**). This edema occurs primarily in the lower extremities and may respond to diuretic therapy. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

### **Male Fertility**

In some cases of in vitro fertilization, nifedipine has been associated with reversible spermatozoal biochemical changes. In vitro studies have shown that nifedipine may inhibit expression of mannose-ligand receptors, thus preventing the spermatozoa from attaching to the zona pellucida and impairing sperm function. In those men who are repeatedly unsuccessful in fathering a child by in vitro fertilization, and where no other explanation could be found, nifedipine should be considered as a possible cause.

### **Use in Elderly**

ADALAT *XL* should be administered cautiously to elderly patients, especially to those with a history of hypotension or cerebral vascular insufficiency.

### **Use in Diabetic Patients**

The use of ADALAT *XL* in diabetic patients may require adjustment for their control.

### **Use in Patients with Impaired Liver Function**

ADALAT XL should be used with caution in patients with impaired liver function (see **ACTION AND CLINICAL PHARMACOLOGY**). A dose reduction, particularly in severe cases, may be required. Close monitoring of response and metabolic effect should apply.

### **Ability to Drive and Use Machines**

Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery, particularly at the start of the treatment, upon changing the medication, or in combination with alcohol.

### **Interaction with Grapefruit Juice**

Published data indicate that through inhibition of cytochrome P-450, flavonoids present in the grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers, including nifedipine (see **ACTION AND CLINICAL PHARMACOLOGY**). Therefore, the administration of nifedipine with grapefruit juice should be avoided.

### **Drug Interactions**

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via the CYP3A4 isoenzyme. Coadministration of nifedipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nifedipine to maintain optimum therapeutic blood levels. If necessary, a reduction in the dose of nifedipine may be considered.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals (ketoconazole, itraconazole, fluconazole), cimetidine, cyclosporine, erythromycin, fluoxetine,

HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), nefazodone, quinidine, terfenadine, and warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, and rifampicin.

Drugs known to be biotransformed via cytochrome P450 include: benzodiazepines, cisapride, flecainide, tacrolimus, theophylline, imipramine and propafenone.

**Beta Adrenergic Blocking Agents:** Concomitant administration of nifedipine and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina. Therefore, caution and careful monitoring of patients on concomitant therapy is recommended (see **INDICATIONS AND CLINICAL USE** and **WARNINGS**).

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

**Long Acting Nitrates:** Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

**Digoxin:** Administration of nifedipine with digoxin may lead to reduced digoxin clearance, and therefore, an increase in the plasma digoxin level. It is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing nifedipine to avoid possible "under-" or "over-"dosing with digitalis.

**Coumarin Anticoagulants:** There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

**Carbamazepine:** No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine. As carbamazepine has 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.

**Quinidine:** The addition of nifedipine to a stable quinidine regimen may reduce the quinidine by 50%, an enhanced response to nifedipine may also occur. The addition of quinidine to a stable nifedipine regimen may result in elevated nifedipine concentrations and a reduced response to quinidine. Some patients have experienced elevated quinidine levels when nifedipine was discontinued. Therefore, patients receiving concomitant therapy of nifedipine and quinidine, or those who had their nifedipine discontinued while still receiving quinidine, should be closely monitored, including determination of plasma levels of quinidine. Consideration should be given to dosage adjustment.

**Quinupristin/Dalfopristin:** Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine. Upon co-administration of both drugs, blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

**Cimetidine and Ranitidine:** Pharmacokinetic studies have shown that concurrent administration of cimetidine or ranitidine with nifedipine results in significant increases in nifedipine plasma levels (ca. 80% with cimetidine, and 70% with ranitidine). Patients receiving either of these drugs concomitantly with nifedipine should be monitored carefully for the possible exacerbation of effects of nifedipine, such as hypotension. Adjustment of nifedipine dosage may be necessary.

**Cisapride:** Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. Upon co-administration of both drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose considered.

**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.

### **ADVERSE REACTIONS**

**Angina:** In 257 chronic stable angina patients treated in controlled and long term open studies with ADALAT XL, adverse effects were reported in 30.0% of patients and required discontinuation of therapy in 8.5% of patients.

The most common adverse effects were: edema (10.1%), headache (3.1%), angina pectoris (3.1%).

The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis:

**Cardiovascular:** Palpitation (2.3%), tachycardia, myocardial infarction, ventricular arrhythmia, extrasystoles, dyspnea, chest pain.

In patients with angina, rarely, and possibly due to tachycardia, nifedipine has been reported to have precipitated an angina pectoris attack. In addition, more serious events were occasionally observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. These events include myocardial infarction, congestive heart failure or pulmonary edema, and ventricular arrhythmias or conduction disturbances.

Central Nervous System: Dizziness (2.3%), hypoesthesia (1.2%), confusion, insomnia, somnolence, nervousness, asthenia, hyperkinesia.

Gastrointestinal: Constipation (1.9%), dyspepsia (1.2%), abdominal pain (1.2%), diarrhea, nausea, melena.

Genito-urinary: Impotence, hematuria, polyuria, dysuria.

Musculo-skeletal: Leg cramps, paresthesia, myalgia, arthralgia.

Dermatologic: Rash, pruritus.

Other: Fatigue (1.2%), pain, periorbital edema.

**Hypertension**: In 661 hypertensive patients treated in controlled trials with ADALAT XL, adverse effects were reported in 54.0% of patients and required discontinuation of therapy in 11.9% of patients. The majority of adverse effects reported occurred within the first three months of therapy.

The most common adverse effects reported with ADALAT XL were edema, which was dose related and ranged in frequency from approximately 10 to 30% in the 30 to 120 mg dose range, headache (16.6%), fatigue (6.2%), dizziness (4.4%), constipation (3.5%), nausea (3.5%).

The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis:

Cardiovascular: Flushing (2.4%), palpitation (2.3%), tachycardia (1.2%), chest pain (1.1%), ventricular arrhythmia, hypotension, syncope.

Central Nervous System: Insomnia (1.8%), nervousness (1.8%), somnolence (1.5%), depression, tremor, decreased libido, migraine, vertigo, amnesia, anxiety, impaired concentration, twitching, ataxia, hypertonia, paresthesia, hypoesthesia.

Gastrointestinal: Dyspepsia (1.5%), flatulence (1.5%), abdominal pain (1.4%), dry mouth (1.1%), diarrhea, vomiting, thirst, melena, eructation, weight increase.

Genito-urinary: Impotence (1.5%), polyuria (1.5%), dysuria, nocturia, oliguria, urinary incontinence, urinary frequency, menstrual disorder.

Musculo-skeletal: Arthralgia, back pain, myalgia.

Special Senses: Abnormal vision, abnormal lacrimation, taste disturbance, conjunctivitis, tinnitus.

Dermatologic: Rash (2.3%), pruritus (1.1%), erythematous rash, alopecia.

Respiratory: Dyspnea (1.7%), bronchospasm, pharyngitis, upper respiratory tract infection, epistaxis.

Other: Leg cramps (2.7%), pain (2.7%), asthenia (2.0%), face edema, gout, allergy, fever, breast pain.

An open, non-randomized postmarketing surveillance study (EXACT), involving 1700 mild to moderate hypertensive patients, was conducted in the offices of general practitioners across Canada. Patients were enrolled in the study if they had been previously treated with either single or dual antihypertensive therapy and the physician considered ADALAT XL an appropriate monotherapy. Patients were to be started on ADALAT XL 30 mg. If after 3 or 6 weeks of therapy with ADALAT XL 30 mg, blood pressure was uncontrolled (i.e., sitting diastolic blood pressure was > 95 mmHg), then the patient was given 60 mg ADALAT XL at the physician's discretion.

Twelve patients were started immediately on ADALAT XL 60 mg. Patients were followed for 20 weeks. Adverse events were reported in 605/1700 patients (35.6%). These adverse events were typical of those seen with the dihydropyridine class of calcium channel blockers (edema, headache, dizziness) and are related to the vasodilatory properties of this class of compounds.

The following is a summary of adverse effects which occurred with a frequency of  $\geq 1\%$  during this 20-week study.

Adverse Effect	All Patients (n = 1700)	
	%	(n)
Patients with $\geq 1$ Adverse Effect	35.6	(605)
Headache	12.2	(207)
Peripheral Edema	8.1	(137)
Dizziness	2.9	(50)
Asthenia	2.8	(48)
Vasodilatation	2.5	(43)
Constipation	2.4	(40)
Palpitations	1.7	(29)
Nausea	1.5	(26)
Anxiety	1.2	(20)
Dyspepsia	1.1	(18)
Insomnia	1.1	(18)
Tachycardia	1.0	(17)

The following table illustrates the time period during which the adverse effects in the preceding table occurred. The majority of the adverse effects occurred during the first 3 weeks that the patients received ADALAT XL. The incidence rate of adverse effects continued to diminish as the length of exposure to ADALAT XL increased.

#### Adverse Effects Occurring During Each Time Period

Adverse Events	Unknown		0 - 3 Weeks		3 - 6 Weeks		6 - 12 Weeks		12 - 20 Weeks	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache	7	(0.7)	148	(13.8)	41	(3.8)	22	(2.1)	6	(0.6)
Peripheral Edema	2	(0.2)	56	(5.2)	42	(3.9)	33	(3.1)	18	(1.7)
Dizziness	2	(0.2)	27	(2.5)	11	(1.0)	7	(0.7)	4	(0.4)
Asthenia	2	(0.2)	23	(2.1)	15	(1.4)	9	(0.8)	0	(0)
Vasodilatation	2	(0.2)	27	(2.5)	5	(0.5)	4	(0.4)	6	(0.6)
Constipation	0	(0)	25	(2.3)	8	(0.7)	5	(0.5)	3	(0.3)
Palpitations	1	(0.1)	17	(1.6)	6	(0.6)	2	(0.2)	4	(0.4)
Nausea	0	(0)	21	(2.0)	4	(0.4)	2	(0.2)	0	(0)
Anxiety	2	(0.2)	5	(0.5)	6	(0.6)	2	(0.2)	6	(0.6)
Dyspepsia	1	(0.1)	5	(0.5)	5	(0.5)	5	(0.5)	2	(0.2)
Insomnia	1	(0.1)	6	(0.6)	3	(0.3)	3	(0.3)	6	(0.6)
Tachycardia	1	(0.1)	5	(0.5)	3	(0.3)	6	(0.6)	3	(0.3)

The following adverse events have been reported with nifedipine rarely.

Rare instances of allergic hepatitis, cholestasis with, or without jaundice have been reported in patients treated with nifedipine.

Gingival hyperplasia similar to that caused by diphenylhydantoin has been reported in patients treated with nifedipine. The lesions usually regressed on discontinuation of the drug. However on occasion, gingivectomy was necessary.

Gynecomastia has been observed rarely in older men on long term therapy, but has so far always regressed completely on discontinuation of the drug.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. Anaphylaxis has been reported rarely.

In postmarketing experience, there have been rare reports of exfoliative dermatitis and Stevens-Johnson Syndrome. Gastrointestinal irritation and gastrointestinal bleeding were also reported, however, the causal relationship is uncertain.

### **Laboratory Tests**

Rare, usually transient, but occasionally significant elevations of enzymes such as CPK, AST, and ALT have been noted. The relationship to drug 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.

An increase (5.4%) in mean alkaline phosphatase was noted in patients treated with ADALAT XL. This was an isolated finding not associated with clinical symptoms and rarely resulted in values which exceeded the upper limit of the normal range.

Serum potassium was unchanged in patients receiving ADALAT XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some 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.

Positive direct Coombs tests, with or without associated hemolytic anemia, have been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to therapy with ADALAT XL is uncertain in most cases, but probable in some.

### **SYMPTOMS AND TREATMENT OF OVERDOSE**

There are several well documented cases of ADALAT XL (nifedipine) overdose. The following symptoms are observed in cases of severe nifedipine intoxication: disturbance of consciousness to the point of coma, a drop in blood pressure, tachycardia/bradycardia, hyperglycemia, 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 ADALAT 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).

Clinically significant hypotension calls for active cardiovascular support including monitoring of cardiac and respiratory function including elevation of extremities and attention to circulating fluid volume and urine output.

Hypotension as a result of arterial vasodilation can also be treated with calcium (10 mL of 10% calcium gluconate solution administered slowly via intravenous route 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 as a last resort only in patients without cardiac arrhythmia or ischemic heart disease and when other safer measures have failed. The dosage of these drugs is determined solely by the effect obtained. Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

Bradycardia and/or bradyarrhythmias have been observed in some cases of nifedipine overdosage. Appropriate clinical measures, according to the nature and severity of the symptoms, should be applied.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **DOSAGE AND ADMINISTRATION**

Dosage should be individualized depending on patient tolerance and response.

ADALAT *XL* (nifedipine) tablets must be swallowed whole and should not be bitten or divided.

In general, titration steps should proceed over a 7-14 day period so that the physician can assess the response to each dose level before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided that the patient is closely monitored.

### **Angina**

Therapy with ADALAT *XL* should normally be initiated with 30 mg once daily. Experience with doses greater than 90 mg daily in patients with angina is limited, therefore, doses greater than 90 mg daily are not recommended.

Angina patients controlled on ADALAT capsules alone or in combination with beta blockers may be safely switched to ADALAT *XL* tablets at the nearest equivalent daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.

### **Hypertension**

Therapy should normally be initiated with 20 or 30 mg once daily. The usual maintenance dose is 30 to 60 mg once daily. Doses greater than 90 mg daily are not recommended.

Patients switched from ADALAT PA 10 or 20 to ADALAT *XL* therapy should receive an initial dosage of ADALAT *XL* no higher than 30 mg once daily, based on previously prescribed dosing regimen. If clinically warranted, the dosage of ADALAT *XL* should be increased to 60 mg once daily. Blood pressure and patient symptoms should be monitored closely following the switch from ADALAT PA to ADALAT *XL*.

No "rebound effect" has been observed upon discontinuation of ADALAT *XL*. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually under close physician supervision.

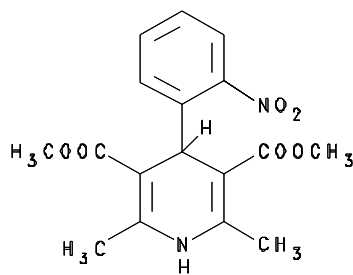
## PHARMACEUTICAL INFORMATION

### (i) DRUG SUBSTANCE

**Proper Name:** nifedipine

**Chemical Name:** 1,4-dihydro-2, 6-dimethyl-4-(o-nitrophenyl)-3,5- pyridine-  
dicarboxylic acid dimethyl ester.

**Structural Formula:**



**Molecular Formula:** C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>

**Molecular Weight:** 346.3

**Description:** Nifedipine is a pyridine dicarboxylic acid dimethylester. It is a fine yellowish powder, practically insoluble in water but soluble in ethanol. It is light-sensitive, and when exposed, is converted to a pharmacologically inactive pyridine derivative via an intramolecular redox process.

**(ii) COMPOSITION**

ADALAT XL is supplied as 20, 30 and 60 mg tablets for oral administration.

ADALAT XL 20, 30 and 60 mg tablets, in addition to the active ingredient nifedipine, contain the following inactive ingredients: cellulose acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, magnesium stearate, pharmaceutical shellac, polyethylene glycol 3350, polyethylene oxide, propylene glycol, red ferric oxide, sodium chloride, synthetic black iron oxide, and titanium dioxide.

**(iii) STABILITY AND STORAGE RECOMMENDATIONS**

Store between 15°C and 30°C. Protect from light and humidity.

**AVAILABILITY OF DOSAGE FORMS**

ADALAT XL (nifedipine) extended release tablets contain nifedipine in strengths of 20 mg, 30 mg and 60 mg.

ADALAT XL 20 mg is a dusty rose tablet imprinted with "ADALAT 20" on one side.

ADALAT XL 20 mg is available in blister packs of 28 and 98 tablets.

ADALAT XL 30 mg is a dusty rose tablet imprinted with "ADALAT 30" on one side.

ADALAT XL 30 mg is now available in blisters of 28 and 98 tablets.

ADALAT XL 60 mg is a dusty rose tablet imprinted with "ADALAT 60" on one side.

ADALAT XL 60 mg is now available in blisters of 28 and 98 tablets.

## **PHARMACOLOGY**

### **ANIMAL PHARMACOLOGY**

#### **In Vitro**

##### **Inhibition of Transmembrane Ca<sup>++</sup> Influx**

Nifedipine has been shown in isolated preparations to restrict the transmembrane calcium ion influx during excitation-contraction coupling in both cardiac and vascular smooth muscles.

In the cat papillary muscle under voltage clamp conditions, nifedipine at a concentration of  $10^{-7}$  to  $10^{-5}$  M did not influence the fast Na<sup>+</sup> inward current, but depressed the slow Ca<sup>++</sup> inward current in a dose-dependent manner without altering the kinetic control mechanism (gating mechanism).

In isolated rabbit ears perfused with tyrode solution, nifedipine has been shown to cause immediate vasodilation, loss of vascular tone and a lack of response to increases in perfusion pressure. However, subsequent neutralization of the drug effect could be achieved by an 8-fold increase in the extracellular Ca<sup>++</sup> concentration.

Studies in vitro using rat thoracic aorta and superior mesenteric artery preparations have shown that nifedipine inhibits contractions induced by potassium and noradrenaline. Tracing the movement of <sup>45</sup>Ca<sup>++</sup> in these preparations showed that nifedipine  $3 \times 10^{-6}$  M reduced the calcium influx triggered by noradrenaline or depolarization. The influx could not be completely blocked and <sup>45</sup>Ca<sup>++</sup> efflux remained unaffected.

##### **Electrophysiologic Effect**

In the isolated guinea-pig atria, the prolongation of the functional refractory period by nifedipine was not very pronounced, although there was a marked decrease in contractility. Even at high concentrations, nifedipine did not affect myocardial excitability.

In the conscious dog, nifedipine produced a moderate, dose-dependent PQ shortening. Only injection of large doses (0.3 to 30  $\mu$ g) of nifedipine into the posterior septal artery induced a

dose-dependent increase in AV conduction. The increase in blood flow through the posterior septal artery required only 1/10 the dose necessary to affect AV conduction.

These electrophysiologic properties of nifedipine explain in part the lack of anti-arrhythmic activity of the drug.

### **In Vivo**

#### **Cardiovascular Effects**

In dogs under opiate analgesia (thereby maintaining practically intact regulation of the circulation), nifedipine administered sublingually at dosages of 10-1000  $\mu\text{g}/\text{kg}$  caused a dose-dependent increase in coronary flow, resulting in an increased oxygen supply to the heart. The peripheral flow, measured in the femoral artery, also increased in a dose-dependent manner. At low doses (10-31.5  $\mu\text{g}/\text{kg}$ ) the cardiac contractility, measured by left ventricular dp/dt, and the end-diastolic pressure were reduced or unaffected, while at higher doses (100-1000  $\mu\text{g}/\text{kg}$ ) there was an increase in dp/dt dependent on the increase in heart rate. Thus low doses of nifedipine may produce a negative inotropic effect, but higher doses produce greater peripheral vasodilation, and the direct negative inotropic effect is modified by the baroreceptor mediated reflex, positive inotropic response and tachycardia.

In further hemodynamic investigations conducted in conscious dogs with implanted aortic flow-probes, a reduction in total peripheral resistance was observed with nifedipine doses of only 10  $\mu\text{g}/\text{kg}$  sublingually, which did not appreciably lower the mean blood pressure. However, a decrease in the mean blood pressure occurred when doses were raised to 31.5 or 100  $\mu\text{g}/\text{kg}$ . In the higher dose range, there were significant decreases in peripheral resistance, with concomitant increases in heart rate, stroke volume and cardiac output as a result of compensatory mechanisms. The drop in peripheral resistance associated with the increase in cardiac output results in a partial transformation of the pressure workload of the heart into a volume workload which is considered to be less oxygen consuming. Lowering of the peripheral resistance also indicated that nifedipine reduces the afterload.

### **Antihypertensive Effects**

In male spontaneously hypertensive rats, nifedipine was administered in single oral doses of 0.3, 1, 3, 6 or 9 mg/kg and compared to hydralazine 2.5, 6, or 7.5 mg/kg (5 animals/group). This was followed by oral administration once a day for ten weeks of nifedipine 1, 3, 6, or 9 mg/kg/day or hydralazine 6 mg/kg/day (5-7 animals/group). No changes in blood pressure were seen after nifedipine 0.3 mg/kg but the 1 and 3 mg/kg doses caused maximal decrease in blood pressure 1-4 hours after administration. Maximal effects of the higher (6 and 9 mg/kg) doses of nifedipine were seen after 15 minutes with a slightly longer duration following 9 mg/kg. The hydralazine dose of 2.5 mg/kg was not observed to have an antihypertensive effect. Significant decreases in blood pressure were seen after 6 and 7.5 mg/kg with maximal effect after 2-4 hours. In the ten-week study, nifedipine at doses of 3 mg/kg/day and above produced significant decreases in blood pressure in the first week and throughout the subsequent weeks to the end of administration. The effect of nifedipine 9 mg/kg/day was comparable to that of hydralazine 6 mg/kg/day.

## **TOXICOLOGY**

### **Acute Toxicity Studies**

<b>Species</b>	<b>Dose Range (mg/kg)</b>		<b>LD50 (mg/kg)</b>	
	<b>Oral</b>	<b>Intravenous</b>	<b>Oral</b>	<b>Intravenous</b>
Mouse	294 - 882	3 - 5	494 (421 - 572)	4.2 (3.8-4.6)
Rat	588 - 1323	10 - 25	1022 (950 - 1087)	15.5 (13.7 - 17.5)
Rabbit	100 - 500	1 - 4	250 - 500	2 - 3
Cat	50 - 250	0.5 - 8	100	0.5 - 8
Dog	250 - 2000	0.5 - 3	>250	2 - 3

Signs of toxicity were usually observed from five to 10 minutes after oral administration and immediately after intravenous administration. These include a reduction of spontaneous motility and apathy in association with increased frequency of respiration usually seen at the lower dosages, with saltatory and clonic spasm, cyanosis and death at the higher dosages. Post-mortem examinations revealed pulmonary edema in rats and cats.

### **Subacute Toxicity Studies**

In rats, oral doses of 0.5 to 100 mg/kg/day nifedipine for 13 weeks did not induce significant adverse effects.

Similar results were obtained in dogs treated with 0.5 to 50 mg/kg/day nifedipine for thirteen weeks.

### **Chronic Toxicity and Carcinogenicity Studies**

Nifedipine was administered orally to dogs at doses of 2.5, 20, and 100 mg/kg/day for 52 weeks. No indication of toxic damage caused by nifedipine was found.

In a two-year study, nifedipine was administered orally to male and female rats in the diet at doses of 5-9, 29-39, and 156-210 mg/kg/day. In the lowest dose group, nifedipine was without toxic effects. The higher doses led to dose-dependent, significant weight losses. An increased mortality was found in the 156-210 mg/kg dose group, especially in the females. The pathological-anatomical examination of the dead animals showed a hypotonia or atonia of the musculature of the small intestine. An increase in the weight of the adrenal glands of male rats was also observed in this dose group. Histopathological examinations revealed no organ damage related to treatment.

At the end of the study, all rats were examined histopathologically with regard to tumorigenesis. Although the animals in the highest dose group showed no uncommon tumour incidence, this group was considered not suitable for comparison with the other treatment groups because of the high mortality rate. No significant differences were found between the controls and the remaining two groups with respect to the frequency, nature, and localization of tumours.

### **Mutagenicity Studies**

In the Dominant Lethal test, the oral administration of nifedipine to mice at a dose of 100 mg/kg for five consecutive days did not affect fertility rate or post-implantation loss.

In the Micronucleus test, two doses of 50 mg/kg or 100 mg/kg nifedipine given orally to mice also did not produce any mutagenic effect. Furthermore, the formation of erythrocytes was not impaired as shown by the polychromatic: normochromatic erythrocyte ratio.

In the Ames' Salmonella/microsome test, nifedipine at doses of up to 12,500  $\mu$ g per plate did not cause any bacteriotoxic effects. Also, a dose-dependent and biologically relevant increase in the number of mutants to a level double that of the negative control was not noted.

### **Reproduction Studies**

Pregnant mice, rats, rabbits were treated orally with 10, 30, and 100 mg/kg nifedipine from Day 6 to Day 15 of gestation.

In the mouse, at doses of 30 and 100 mg/kg, there was an increase in the number of fetal resorptions. Fetal malformations in the form of cleft palate and rib deformities occurred at all dose levels in a dose related fashion (cleft palate occurred in 5/218 controls, 13/190 at 10 mg/kg, 22/112 at 30 mg/kg and 3/3 at 100 mg/kg).

In the rat, the dose of 30 mg/kg was not toxic to pregnant dams, but caused reduced fetal weight and increased fetal loss. The dose of 100 mg/kg produced malformations in the fetuses from 20 percent of the mother animals. In a total of 11 fetuses, 10 showed malformation of the front or hind paws (ectrodactyly, oligodactyly and adactyly) and one developed a severe malformation of the sinciput.

In the rabbit, there was dose-dependent anorexia and weight loss in mothers during the dosing period. At 30 and 100 mg/kg reduced litter size and weight and increased fetal loss were evident.

Studies on pregnant rhesus monkeys with oral doses of 2 (1 animal) or 6 mg/kg/day (4 animals) revealed no teratogenic effects. The placentas were poorly developed in these animals.

Pre- and post-natal studies on rats with daily doses of 3, 10, 30 and 100 mg/kg showed that nifedipine caused significant prolongation of the gestation period at dosages of 10 mg/kg upwards and a decrease in litter size. The post-natal development of the newborn animals was

impaired when doses of 30 mg/kg or more had been administered. All offspring in the 100 mg/kg group died.

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## CONSUMER INFORMATION

### Pr ADALAT® XL®

Nifedipine extended-release tablets Bayer Standard

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ADALAT XL. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

ADALAT® XL® (nifedipine extended-release tablets) is used for:

#### ***High Blood Pressure***

There are two numbers used for measuring blood pressure: systolic and diastolic. The systolic number (stated first) represents the maximum pressure of the heart muscle contraction while the heart is beating. The diastolic number (listed second) measures the basic resting pressure when the heart is refilled between beats.

Blood pressure readings lower than 120 mmHg systolic and 80 mmHg diastolic are considered to be normal for adults. Patients with values above 139 mmHg systolic and 89 mmHg diastolic are regarded as having high blood pressure.

ADALAT XL may be used in patients to manage mild to moderate high blood pressure.

#### ***Stable Angina***

Angina is chest pain or discomfort that occurs when your heart muscle does not get enough blood. Angina may feel like pressure or a squeezing pain in your chest. The pain may also occur in your shoulders, arms, neck, jaw, or back. It may also feel like indigestion.

Angina is a symptom of coronary heart disease (CAD), the most common type of heart disease. CAD occurs when plaque builds up in the coronary arteries. This buildup of plaque is called atherosclerosis. As plaque builds up, the coronary arteries become narrow and stiff. Blood flow to the heart is reduced. This decreases the oxygen supply to the heart muscle.

Stable angina is the most common type of angina. It occurs when the heart is working harder than usual.

ADALAT XL may be used in patients to manage chronic stable angina.

#### What it does:

ADALAT XL manages high blood pressure and chronic stable angina. It is called a “calcium channel blocker”. Although the mechanism by which ADALAT XL reduces blood pressure and relieves angina is not fully known, it is believed to be brought about as a result of the ability of ADALAT XL to widen and relax blood vessels.

#### When it should not be used:

You should not use ADALAT XL if the following applies:

- you have had an allergic reaction to nifedipine or to any of the nonmedicinal ingredients (see What the nonmedicinal ingredients are)
- you are pregnant, breastfeeding, or a woman of childbearing age
- you have severe low blood pressure
- you are taking the medicine rifampicin

See also **SIDE EFFECTS AND WHAT TO DO ABOUT THEM.**

#### What the medicinal ingredient is:

ADALAT XL contains nifedipine.

#### What the nonmedicinal ingredients are:

ADALAT XL also contains cellulose acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, magnesium stearate, pharmaceutical shellac, polyethylene glycol 3350, polyethylene oxide, propylene glycol, red ferric oxide, sodium chloride, synthetic black iron oxide, and titanium dioxide.

#### What dosage forms it comes in:

The medication in ADALAT XL is packed within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it.

ADALAT XL comes in strengths of 20 mg, 30 mg, or 60 mg tablets. ADALAT XL tablets are dusty rose.

## WARNINGS AND PRECAUTIONS

Reactions to the drug in ADALAT *XL* vary from person to person. This may impair your ability to drive or to operate machinery, particularly at the start of treatment, when changing the medication, or in combination with alcohol.

Your doctor will have asked you many questions about your health, lifestyle, and medications before recommending ADALAT *XL*. That is why it is very important that you tell your doctor all such information.

If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine (or any medicine):

- you are pregnant or breastfeeding
- you have heart failure, liver disease, kidney disease, or coronary artery disease
- you have unstable angina (sudden chest pain that occurs at rest and gets increasingly worse)
- you have recently had a heart attack or you have a heart condition called aortic stenosis (narrowing of a valve in your heart)
- you have pre-existing gastrointestinal narrowing disease
- you have diabetes
- you have a history of poor blood circulation in the brain

## INTERACTIONS WITH THIS MEDICATION

Some medicines may interact with ADALAT *XL*. Let your healthcare professional know what other medicines (including over-the-counter medicines, vitamins, and herbal products) you are taking.

If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine (or any medicine) if you are receiving:

- azole antifungals (ketoconazole, itraconazole or fluconazole)
- cyclosporine
- carbamazepine
- cimetidine
- diltiazem
- digoxin
- erythromycin
- fluoxetine
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, or amprenavir)
- nefazodone
- phenobarbital

- phenytoin
- quinidine
- quinupristin/dalfopristin
- tacrolimus
- rifampicin
- valproic acid

DO NOT eat grapefruit or drink grapefruit juice while you are using this medicine.

## PROPER USE OF THIS MEDICATION

### Usual Dose

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Follow your doctor's treatment plan exactly so that you reach and maintain your blood pressure targets, and get relief from angina. Do not use more medicine or use it more often than your doctor tells you to.

You can take this medication with or without food.

Do not discontinue a medication on your own. If you have a problem with a drug, always tell your doctor.

You must swallow ADALAT *XL* tablets whole. Do not chew, divide or crush the tablets. This can result in a large immediate release of the drug.

The medication in ADALAT *XL* is packed within a nonabsorbable shell that has been specially designed to slowly release the drug over 18 hours so that the body can absorb it. The shell will pass into your stool after your body has absorbed the medicine. This is normal and is nothing to worry about.

See also **ABOUT THIS MEDICATION**: When it should not be used; and **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

### Missed Dose

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose unless instructed by your doctor.

**Overdose**

In case of accidental overdose contact a healthcare practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

ADALAT XL can cause unwanted side effects. The most common side effects include swelling of tissues (edema), headaches, chest pain (angina pectoris), low blood pressure, dizziness, nausea, and constipation.

You should call your doctor if you experience any of the following:

- nausea
- vomiting

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency treatment
		Only if severe	In all cases	
Common	Wheezing or trouble breathing			✓
	Chest tightness, chest pain (angina pectoris)			✓
	Abdominal cramps		✓	
	Vomiting		✓	
	Diarrhea		✓	
	Irregular heartbeat			✓

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency treatment
		Only if severe	In all cases	
Uncommon	Allergic reactions: difficulty breathing or swallowing, rash or hives (redness, intense itching and burning), swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs			✓
	Constipation		✓	

*This is not a complete list of side effects. For any unexpected effects while taking ADALAT XL, contact your doctor or pharmacist.*

**HOW TO STORE IT**

ADALAT XL should be stored at room temperature (15-30°C). Protect from light and humidity.

Keep all medicine away from children and never share your medicine with anyone.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

Fax toll-free to 1-866-678-6789, or

Mail to: Canada Vigilance Program

Health Canada

Postal Locator 0701C

Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained at <http://www.bayer.ca> or by contacting the sponsor, Bayer Inc., at: 1-800-265-7382 or [canada.medinfo@bayer.com](mailto:canada.medinfo@bayer.com).

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