SCHEDULING STATUS: S3

PROPRIETARY NAMES AND DOSAGE FORM:

ADALAT® XL 20
Controlled Release tablet
ADALAT® XL 30
Controlled Release tablet
ADALAT® XL 60
Controlled Release tablet

COMPOSITION:

Each ADALAT XL 20 tablet contains 20 mg nifedipine
Each ADALAT XL 30 tablet contains 30 mg nifedipine
Each ADALAT XL 60 tablet contains 60 mg nifedipine

Excipients: Cellulose acetate, ferric(III) oxide (E 172), hydroxypropyl cellulose, macrogol 3350, macrogol 200000, macrogol 5 million, magnesium stearate, hydroxypropyl methylcellulose, sodium chloride, propylene glycol, titanium(IV) oxide (E 171).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1. Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Nifedipine, a calcium channel blocker, improves oxygen supply to the myocardium with simultaneous decrease of oxygen requirements. Nifedipine has a vasodilatory effect on the peripheral arterial beds causing a fall in peripheral vascular resistance and an increase in peripheral blood flow. Ca^{2+}-channel blockers are useful in low-renin hypertension. Nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium. The bioavailability of the 20 mg tablet is proportional to that of the 30 mg tablet.

Pharmacokinetic properties:

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

Absorption:
After oral administration nifedipine is almost completely absorbed. At steady state the bioavailability of nifedipine in ADALAT XL tablets ranges from 68 to 86 % relative to nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of medicine availability.

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

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

Nifedipine is excreted in the form of its metabolites predominantly via the kidneys, and about 5 to 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0,1 %) in the urine.

Elimination:
The terminal elimination half-life is 1,7 to 3,4 hours in conventional formulations (nifedipine capsules). The terminal half-life after ADALAT XL does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption.

Special Populations:
In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers.
In cases of impaired liver function the total clearance is reduced (see Contra-indications).

INDICATIONS:

Treatment of mild to moderate hypertension
Prophylaxis of chronic stable angina pectoris

CONTRA-INDICATIONS:

ADALAT XL is contra-indicated in pregnancy and during breastfeeding (see: Pregnancy and lactation).
ADALAT XL must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients.
ADALAT XL must not be used in cardiovascular shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg), in cases of manifest heart failure and in the case of severe aortic stenosis.

Owing to the duration of action of the formulation, ADALAT XL should not be administered to patients with hepatic impairment.

ADALAT XL should not be administered to patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract.
ADALAT XL must not be used in patients with a Kock pouch (ileostomy after proctocolectomy).
ADALAT XL is contra-indicated in patients with inflammatory bowel disease.
ADALAT XL is contra-indicated in combination with rifampicin because effective plasma levels of nifedipine may not be obtained because of enzyme induction by rifampicin (see Interactions).

WARNINGS AND SPECIAL PRECAUTIONS:

Grapefruit juice inhibits the metabolism of ADALAT XL. After regular intake of grapefruit juice the blood pressure lowering 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 ADALAT XL (see Interactions).

The following medicines are known to either inhibit or to induce cytochrome P450 3A4 system and may therefore alter the first pass or clearance of nifedipine:

Digoxin, phenytoin, quinidine, quinupristin, dalfopristin, cimetidine, rifampicin, diltiazem, cisapride, erythromycin, fluoxetine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, fluconazole, nefazodone, tacrolimus, carbamazepine, phenobarbitone and valproic acid.

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

Co-administration of ADALAT XL with i.v. magnesium sulfate may cause an excessive fall in blood pressure.

Safety of nifedipine as tocolytic agent and in the treatment of hypertension in pregnancy after 20 weeks has not been established. Harm to the foetus cannot be excluded.

Although a "steal" effect has not been demonstrated, ADALAT XL therapy should be discontinued in patients experiencing this effect.
ADALAT XL should not be switched once a patient has been stabilised, without appropriate monitoring.

Care should be exercised in dialysis patients with malignant hypertension and irreversible kidney failure with hypovolaemia as a marked fall in blood pressure may occur.
Caution should be exercised in angina patients with hypotension, in cases of manifest heart failure and in the case of severe aortic stenosis.
ADALAT XL should be used with caution in patients with a poor cardiac reserve.

A transient increase in blood glucose has been noted. Care must be taken in patients with diabetes mellitus.

In single cases obstructive gastrointestinal symptoms have been described without known history of gastrointestinal disorders. Bezoars can occur in rare cases and may require surgical intervention.
ADALAT XL must not be used in patients with 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).
There are no recommendations for use in children.

In single cases of *in vitro* fertilization, nifedipine has been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilization and if no other explanation can be found, nifedipine should be considered a possible reason.

ADALAT XL can enhance or supplement the action of blood pressure lowering preparations such as beta-receptor blockers and diuretics. An additive effect resulting in postural hypotension should be borne in mind. Blood pressure should be monitored carefully during initiation and upward titration of ADALAT XL especially if patients are on antihypertensive therapy.

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

Effect on ability to drive and use machines:

Reactions to ADALAT XL, 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 the treatment, on changing the medication and in combination with alcohol.

INTERACTIONS:

ADALAT XL is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of ADALAT XL.
The extent as well as the duration of interactions should be taken into account when administering ADALAT XL together with the following medicines:

- *Rifampicin*
  Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of ADALAT XL is distinctly reduced and thus its efficacy weakened. The use of ADALAT XL in combination with rifampicin is therefore contra-indicated.

Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and if necessary, a reduction in the ADALAT XL dose considered.

- *Erythromycin*
  Erythromycin is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore the potential for an increase of ADALAT XL plasma concentrations upon co-administration of both medicines cannot be excluded.

- *Amprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir*
  A clinical study investigating the potential of an interaction between ADALAT XL and amprenavir, indinavir, nelfinavir, ritonavir or saquinavir has not yet been performed. Medicines of this class are known to inhibit the cytochrome P450 3A4 system.

  In addition, indinavir and ritonavir have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of ADALAT XL. When administered together with ADALAT XL, a substantial increase in plasma concentrations of ADALAT XL due to a decreased first pass metabolism and a decreased elimination cannot be excluded. Upon co-administration, the blood pressure should be monitored and if necessary, a reduction in the ADALAT XL dose considered.

- *Ketoconazole, Itraconazole, Fluconazole*
  Medicines of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with ADALAT XL, a substantial increase in systemic bioavailability of ADALAT XL due to decreased first pass metabolism cannot be excluded. Upon co-administration, the blood pressure should be monitored and if necessary, a reduction in the ADALAT XL dose considered.

- *Fluoxetine*
  Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of ADALAT XL. Therefore an increase of ADALAT XL plasma concentrations upon co-administration of both medicines cannot be excluded. When fluoxetine is given together with ADALAT XL, the blood pressure should be monitored and if necessary, a reduction in the ADALAT XL dose considered.

- *Nefazodone*
  A clinical study investigating the potential of a medicine interaction between ADALAT XL and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines.

  Therefore an increase of ADALAT XL plasma concentrations upon co-administration of both medicines cannot be excluded. When nefazodone is given together with ADALAT XL, the blood pressure should be monitored and if necessary, a reduction in the ADALAT XL dose considered.

- *Quinupristin/Dalfopristin*

Simultaneous administration of quinupristin/dalfopristin and ADALAT XL may lead to increased plasma concentrations of ADALAT XL. Upon co-administration of both medicines, the blood pressure should be monitored and if necessary, a reduction of the ADALAT XL dose considered.

- *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 ADALAT XL plasma concentrations and hence an increase in efficacy cannot be excluded.

- *Cimetidine*
  Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of ADALAT XL and may potentiate the antihypertensive effect.

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

- *Phenytoin:*
  Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of ADALAT XL is reduced and thus its efficacy weakened. When both medicines are concomitantly administered, the clinical response to ADALAT XL should be monitored and if necessary, an increase of the ADALAT XL dose considered.

  If the dose of ADALAT XL is increased during co-administration of both medicines, a reduction of the ADALAT XL dose should be considered when the treatment with phenytoin is discontinued.

- *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 ADALAT XL plasma concentrations and hence a decrease in efficacy cannot be excluded.

- *Phenobarbitone:*
  As phenobarbitone has been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in ADALAT XL plasma concentrations and hence a decrease in efficacy cannot be excluded.

Effects of ADALAT XL on other medicines:

ADALAT XL may exacerbate the blood pressure lowering effect of concomitantly applied antihypertensive, such as:

- diuretics
- β-blockers
- ACE-inhibitors
- Angiotensin receptor blockers
- Other calcium channel blockers
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa.

- When ADALAT XL is administered simultaneously with ß-receptor blockers the patient should be carefully monitored, since fairly severe hypotension may occur. Deterioration of heart failure is also known to develop in isolated cases.

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

- *Quinidine*
  When ADALAT XL and quinidine were administered simultaneously, lowered quinidine or, after discontinuation of ADALAT XL, a distinct increase in plasma concentrations of quinidine has been observed. For this reason, when ADALAT XL is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose is recommended.

  Increased plasma concentrations of ADALAT XL have been reported upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of ADALAT XL. Therefore, the blood pressure should be carefully monitored if quinidine is added to an existing therapy with ADALAT XL. If necessary, the dose of ADALAT XL should be decreased.

- *Tacrolimus*
  Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Upon co-administration of tacrolimus and ADALAT XL, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

- *Diltiazem*
  Diltiazem decreases the clearance of ADALAT XL. ADALAT XL increases the bioavailability and decreases the clearance of diltiazem. The combination of both medicines should be administered with caution and a reduction of both doses may be considered.

Medicine - food interactions*:*

- *Grapefruit Juice*
  Grapefruit juice inhibits the metabolism of ADALAT XL. Administration of ADALAT XL together with grapefruit juice thus results in elevated plasma concentrations of ADALAT XL due to a decreased first pass metabolism in the GIT. As a consequence, the blood pressure lowering effect may be increased (see Warnings and Special precautions).

Other forms of interactions:

- ADALAT XL may cause falsely increase spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

PREGNANCY AND LACTATION:

ADALAT XL is contra-indicated in pregnancy and during lactation (see Contraindications).
Mothers taking ADALAT XL should not breastfeed their babies, and mothers breastfeeding their babies should not take ADALAT XL as nifedipine passes into breastmilk.

Co-administration of ADALAT XL with i.v. magnesium sulfate may cause an excessive fall in blood pressure which could harm both mother and foetus.

Preclinical and animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects when administered during any stage of pregnancy, and decreased neonatal survival after birth. Only a life-

threatening hypertensive crisis of the mother in the late trimester of pregnancy, who is not responding to any other treatment, may override this contraindication.

DOSAGE AND DIRECTIONS FOR USE:

Method of administration:
Oral use.

The tablets should be swallowed whole with a glass of fluid; under no circumstances should they be bitten, chewed or broken up. Grapefruit juice is to be avoided.

The tablets should be taken at approximately 24 hour intervals, i.e. at the same time each day, preferably during the morning. ADALAT XL may be taken irrespective of meal times.

The recommended initial dose is one 30 mg tablet once daily. A starting dose of 20 mg may be considered when medically indicated, such as the elderly, may benefit from initiation of therapy at 20 mg once daily. If necessary, the dosage can be increased according to individual requirements up to a maximum of 90 mg once daily.

In general, titration steps should proceed over a 7 to 14 day period so that the response to each dose level can be assessed before proceeding to higher doses.

Additional information on special populations:

Children and adolescents:
The safety and efficacy of ADALAT XL in children below 18 years has not been established.

Geriatric patients:
Based on pharmacokinetic data for ADALAT XL no dose adaptation in elderly people above 65 years is necessary.

Patients with hepatic impairment:
Owing to the duration of action of the formulation, ADALAT XL should not be administered to patients with hepatic impairment (see Contra-indications).

Patients with renal impairment:
Based on pharmacokinetic data no dosage adjustment is required in patients with renal impairment.

SIDE 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 %).
The frequencies of ADRs reported with nifedipine-containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10000 to < 1/1000).

System Organ Class	**Common**	**Uncommon**	**Rare**
Immune System Disorders		Allergic reaction Allergic oedema/angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash

System Organ Class	Common	Uncommon	Rare
Psychiatric Disorders		Anxiety reactions Sleep disorders	
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor Somnolence	Paraesthesia Dysaesthesia
Eye Disorders	Eye pain	Visual disturbance	Amblyopia
Cardiac Disorders		Tachycardia Palpitations	Chest pain (angina pectoris)
Vascular Disorders	Oedema Vasodilation	Hypotension Syncope	
Respiratory, Thoracic and Mediastinal Disorders		Nosebleed Nasal congestion	
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Vomiting Nausea Dyspepsia Flatulence Dry mouth Gastro-oesophageal reflux	Gingival hyperplasia
Hepatobiliary Disorders		Transient increase in liver enzymes	
Skin and Subcutaneous Tissue Disorders		Erythema	Palpable purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling Arthralgia Myalgia	
Renal and Urinary Disorders		Polyuria Dysuria	
Reproductive System Disorders		Erectile dysfunction	
General Disorders	Feeling unwell	Unspecific pain Chills	

*may result in life-threatening outcome

The ADRs identified only during the on-going postmarketing surveillance, and for which a frequency could not be estimated, are listed below:

System Organ Class	Frequency Unknown
Blood and Lymphatic system disorders	Agranulocytosis
Immune system disorders	Anaphylactic/anaphylactoid reaction
Metabolism and nutrition disorders	Hyperglycaemia

System Organ Class	Frequency Unknown
Nervous system disorders	Hypoaesthesia
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Bezoar dysphagia Intestinal obstruction, Intestinal ulcer Vomiting Jaundice
Hepatobilliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Toxic Epidermal Necrolysis Photosensitivity allergic reaction
Endocrine disorders	Gynaecomastia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Flushing, headaches, severe hypotension, increase or decrease in heart rate, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema and unconsciousness to the point of coma have been observed.

If these symptoms are observed in time, the first therapeutic measure to be considered is gastric lavage with added medicinal charcoal, 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 ADALAT XL is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Treatment is symptomatic and supportive.

Bradycardiac heart rhythm disturbances may be treated symptomatically with ß-sympathomimetics and in life-threatening bradycardiac disturbances of heart rhythm, temporary pacemaker therapy is advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation may be treated with calcium (10 - 20 ml of a 10 % calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium may reach the upper normal to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or norepinephrine (noradrenaline) may be administered additionally. 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.

IDENTIFICATION:

Round, convex, pink coated tablet with a laser hole on one side and marked in black printed text: ADALAT 20, ADALAT 30 or ADALAT 60.

PRESENTATION:

Blister packs composed of PP/Alu foil, PVC/ PVDC foil or PA/Al/PVC foil backed with aluminium foil containing 28 or 30 tablets packed in a cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.
Protect from light and moisture.
Not to be removed from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ADALAT XL 20: A39/7.1/0634
ADALAT XL 30: Y/7.1/314
ADALAT XL 60: Y/7.1/315

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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