SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adipine XL 30 mg Tablets
Adipine XL 60 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Adipine XL 30mg Tablets
Each tablet contains 30mg of nifedipine

Adipine XL 60mg Tablets
Each tablet contains 60mg of nifedipine

3 PHARMACEUTICAL FORM

Adipine XL 30mg Tablets
Prolonged release tablet
Each pale red tablet is round and biconvex and embossed with "30" on one side.

Adipine XL 60mg Tablets
Prolonged release tablet
Each pale red tablet is round and biconvex and embossed with "60" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The tablets are indicated for :
- the treatment of all grades of hypertension
- the prophylaxis of chronic stable angina pectoris, either as monotherapy or in combination with a beta-blocker

4.2 Posology and method of administration

Posology
In mild to moderate hypertension, the recommended initial dose is one 20 mg tablet once-daily. In severe hypertension, the recommended initial dose is one 30 mg tablet once-daily. If necessary, the dosage can be increased according to individual requirements up to a maximum of 90 mg once-daily.

For the prophylaxis of angina pectoris, the recommended initial dose is one 30 mg tablet once-daily. The dosage can be increased according to individual requirements up to a maximum of 90 mg once-daily.

Prophylactic antianginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Adipine XL. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30 mg Adipine XL once-daily. Subsequent titration to a higher dose may be initiated as warranted clinically.

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see section 4.5).

Duration of treatment
Treatment may be continued indefinitely.

Additional information on special populations
Paediatric population
The safety and efficacy of Adipine XL in children below 18 years has not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1

Elderly
Based on pharmacokinetic data for Adipine XL no dose adaptation in elderly people above 65 years is necessary.

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

Method of administration
Oral use.
The tablets should be swallowed whole with a glass of water, either with or without food. The tablets should be taken at approximately 24-hour intervals, i.e. at the same time each day, preferably during the morning. Adipine XL tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Adipine XL should not be taken with grapefruit juice (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Nifedipine XL Tablets are contraindicated:
- in patients with a known hypersensitivity to the drug or other constituents of the tablets
- in patients with a known hypersensitivity to other dihydropyridines calcium antagonists, because of the theoretical risk of cross-reactivity

- in women who are or may become pregnant, are capable of child bearing or to nursing mothers
- in patients with clinically significant aortic stenosis, in cardiogenic shock or unstable angina or for the treatment of acute attacks of angina
- in patients with inflammatory bowel disease, Crohn's disease or with a history of gastrointestinal obstruction, oesophageal obstruction or with decreased diameter of the gastrointestinal lumen
- in patients with hepatic impairment
- for secondary prevention of myocardial infarction or during or within one month of a myocardial infarction

Nifedipine XL Tablets should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.5).

The safety of nifedipine prolonged release tablets has not been established in patients with malignant hypertension.

4.4 Special warnings and precautions for use

Adipine XL tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

Caution should be exercised in patients with hypotension as there is a risk of further reduction in blood pressure and care must be exercised in patients with very low blood pressure (severe hypotension with systolic blood pressure less than 90 mm Hg).

Adipine XL should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Adipine XL should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.6).

Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy, refer to section 4.6.

Adipine XL is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see section 4.6).

In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Adipine XL may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind Nifedipine XL will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Adipine XL should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Diabetic patients taking Adipine XL may require adjustment of their control.

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see section 4.5).

Drugs, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:
- 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.

As the outer membrane of the Adipine XL tablet is not digested, what appears to be the complete tablet may be seen in the toilet or associated with the patient's stools. Also, as a result of this, care should be exercised when administering Adipine XL to patients, as obstructive symptoms may occur**.** Bezoars can occur in very rare cases and may require surgical intervention

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

A false positive effect may be experienced when performing a barium contrast x-ray.

For use in special populations see section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

Known Interactions

Nifedipine should not be taken with grapefruit juice because bioavailability is increased.

Cimetidine may potentiate the antihypertensive effect of nifedipine tablets if it is administered simultaneously.

It is reported that serum quinidine levels have been reduced when it is used in combination with nifedipine, irrespective of the quinidine dose taken.

The administration of nifedipine and digoxin concurrently may lead to reduced digoxin clearance and therefore, bring about an increase in the plasma digoxin level. Close monitoring of plasma digoxin levels should take place and, if necessary, a reduction in the dosage of digoxin.

Phenytoin induces the cytochrome P450 3A4 system. When nifedipine is co-administered with phenytoin, nifedipine's bioavailability is reduced and consequently, its efficacy is weakened. In such cases, the clinical response to nifedipine should be monitored following concomitant administration and, if necessary, consideration should be given to increasing the nifedipine dose. If the nifedipine dose is increased

during the co-administration of both drugs, consideration should be given to reducing the nifedipine dose when phenytoin therapy is discontinued.

Diltiazem decreases the clearance of nifedipine and hence increases plasma nifedipine levels. Caution should be exercised when both drugs are given simultaneously. A reduction of nifedipine dose may be required when the two are used together.

Nifedipine may falsely increase the spectrophotometric values of urinary vanillylmandelic acid. HPLC measurements are not affected.

Nifedipine should not be administered concomitantly with rifampicin, as effective plasma levels of nifedipine may not be achieved as a result of enzyme induction.

Simultaneous administration of cisapride and nifedipine or quinupristin/dalfopristin and nifedipine may lead to increased plasma concentration of nifedipine. Hence, the blood pressure may need to be monitored and a reduction in the nifedipine dose may be necessary.

Nifedipine enhances the effect of non-polarising muscle relaxants.

Theoretical Interactions
Nifedipine is metabolised via the cytochrome P450 3A4 system. Therefore, there are theoretical interactions with drugs such as erythromycin, ketoconazole, itraconazole, fluconazole, fluoxetine, indinavir, nelfinavir, ritonavir and saquinavir that are known to inhibit this enzyme system. Although no *in vivo* interaction studies with these drugs have been carried out, their co-administration with nifedipine *in vitro*, have shown increases in nifedipine plasma concentrations. Therefore, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose should be considered.

Similarly, the potential interaction between nifedipine and nefazodone has not been clinically investigated. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs and therefore, co-administration with nifedipine may increase the plasma concentrations of nifedipine. Again, monitoring of the blood pressure is advised when both drugs are simultaneously administrated with, if necessary, a reduction in the nifedipine dose.

Tacrolimus is metabolised via the cytochrome P450 3A4 system. Upon co-administration with nifedipine, the plasma levels of tacrolimus should be monitored and, if necessary, consideration should be given to reducing the tacrolimus dose.

Carbamazepine, phenobarbital or valproic acid have been shown to alter the plasma levels of a structurally similar calcium channel blocker, however, no interactive studies have been carried out with these drugs and nifedipine. A decrease (with carbamazepine or phenobarbital) or an increase (with valproic acid) in nifedipine plasma concentrations, leading to a change in efficacy, can therefore not be ruled out.

Drugs Shown Not to Interact With Nifedipine
Aspirin, benazepril, candesartan cilexetil, debrisoquine, doxazosin, irbesartan, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone and triamterene hydrochlorothiazide are drugs known not to affect the pharmacokinetics of nifedipine when they are administered concomitantly with nifedipine.

4.6 Fertility, pregnancy and lactation
Pregnancy

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine (see section 4.4).

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

There are no adequate well controlled studies in pregnant women.

From the clinical evidence available a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

Breast-feeding
Nifedipine is excreted in the breast milk. The nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breast-feeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant (see section 4.4).

Fertility
In single reports of in vitro fertilisation, calcium antagonists like nifedipine have been associated with biochemical alterations in the head of the spermatozoa that may impair sperm function. Calcium antagonists like nifedipine should be considered as possible causes in those men who are repeatedly unsuccessful in fathering a child by in vitro fertilisation and where no other explanation can be found.

4.7 Effects on ability to drive and use machines

Reactions to nifedipine may vary in intensity in patients, especially at the onset of therapy, on changing medication or when combined with alcohol. Therefore, the patient should be warned of the possible effects and advised not to drive or operate machinery, if affected.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

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 (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under “Not known”.

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Not Known**
Blood and Lymphatic System Disorders				Agranulocytosis Leucopenia
Immune System Disorders		Allergic reaction Allergic oedema/angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric Disorders		Anxiety reactions Sleep disorders		
Metabolism and Nutrition Disorders				Hyperglycaemia
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/Dysaesthesia	Hypoaesthesia Somnolence
Eye Disorders		Visual disturbances		Eye pain
Cardiac Disorders		Tachycardia Palpitations		Chest pain (Angina pectoris)
Vascular Disorders	Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic, and Mediastinal Disorders		Nosebleed Nasal congestion		Dyspnoea Pulmonary oedema**
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting Gastroesophageal sphincter insufficiency

Hepatobiliary Disorders		Transient increase in liver enzymes		Jaundice
Skin and Subcutaneous Tissue Disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal and Connective Tissue Disorders		Muscle cramps Joint swelling		Arthralgia Myalgia
Renal and Urinary Disorders		Polyuria Dysuria		
Reproductive System and Breast Disorders		Erectile dysfunction		
General Disorders and Administration Site Conditions	Feeling unwell	Unspecific pain Chills		

* = may result in life-threatening outcome
** cases have been reported when used as tocolytic during pregnancy (see section 4.6)

There have also been reports of gynaecomastia in older men on long-term therapy, but this usually regresses when treatment is withdrawn.

Myocardial infarction is also known to occur although it is not possible to distinguish it from the natural course of ischaemic heart disease.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

There are few reports of nifedipine overdose and the symptoms are not necessarily dose-related. The most likely manifestations of overdose are severe hypotension due to vasodilatation, tachycardia or bradycardia.

The metabolic disturbances may include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia. The cardiac effects, which may occur, include heart block, AV dissociation and asystole and cardiogenic shock with pulmonary oedema.

Other toxic effects include drowsiness, dizziness, confusion, nausea, vomiting, lethargy, flushing, hypoxia, unconsciousness and coma.

Management

In the treatment of overdose it is important to restore stable cardiovascular conditions as soon as possible and achieve total elimination of nifedipine.

Gastric lavage and charcoal instillation may be of assistance if the patient is found early after the overdose. Gastric lavage may be necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

To prevent the subsequent absorption of nifedipine, elimination must be complete, including from the small intestine.

Activated charcoal should be given in 4 hourly doses of 25g for adults and 10g for children. The blood pressure, central arterial pressure, ECG, electrolytes, pulmonary wedge pressure and urea should be carefully monitored.

Placing the patient in the supine position with the feet raised and the use of plasma expanders, as appropriate, should treat the hypotension resulting from cardiogenic shock and arterial vasodilatation. If these measures are ineffective, hypotension may be treated with 10ml to 20ml of 10% calcium gluconate, administered intravenously over a period of 5 to 10 minutes. If ineffective, the therapy can be continued, with ECG monitoring.

Also, beta-sympathomimetics may be given eg., 0.2mg of isoprenaline by slow intravenous or 5 µg per minute as a continuous infusion. If the blood pressure response is inadequate with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The patient's response should determine the dosage of these drugs.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker.

Additional fluid should be administered with caution to avoid cardiac overload.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anatomical Therapeutic Chemical (ATC) code: C08C A05

Selective calcium channel blocker

(dihydropyridine derivative), with mainly vascular effects

Nifedipine is a dihydropyridine and is a specific and potent antagonist of calcium influx through the slow channel of the cell membrane of cardiac and smooth muscle cells, both in coronary and peripheral circulation.

The antihypertensive effects of nifedipine are achieved by causing peripheral vasodilatation resulting in a reduction in peripheral resistance. Nifedipine administered once daily provides twenty-four hours control of elevated blood pressure. Nifedipine reduces blood pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect.

Nifedipine produces its effects in the treatment of angina by reducing peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume and causing a decrease in after-load. Also, nifedipine submaximally dilates clear and atherosclerosis coronary arteries to protect the heart against coronary artery spasm and improve perfusion to the ischaemic myocardium. Nifedipine decreases the frequency of painful attacks and the ischaemic ECG changes regardless of the relative contribution from coronary artery spasm or atheroschlerosis.

Paediatric population

Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with different formulations in different dosages. Antihypertensive effects of nifedipine have been demonstrated but dose recommendations, long term safety and effect on cardiovascular outcome remain unestablished. Paediatric dosing forms are lacking.

5.2 Pharmacokinetic properties

General Characteristics

Nifedipine XL Tablets are formulated as prolonged release products. They are designed to control the release of nifedipine over twenty-four hours so that a clinical effect is achieved when the tablets are swallowed, once a day.

The pharmacokinetic profile is characterised by low peak-trough fluctuation. Over twenty-four hours plasma concentration versus time profiles at steady state are plateau-like, rendering the Nifedipine XL Tablets suitable for once daily administration.

Absorption

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. However due to extensive hepatic first pass

metabolism in the liver, the resultant bioavailability lies between 45 % and 68 %. The absorption rate is slightly changed when the tablets are taken after ingesting food but the extent of drug availability is not affected.

Distribution

Nifedipine is about 95 % bound to plasma proteins.

Metabolism

Nifedipine is almost completely metabolised in the liver by oxidative and hydrolytic processes.

Elimination

The elimination half-life is 2 to 5 hours. About 70 % to 80 % of the administered dose of nifedipine is excreted via the kidneys, mostly as its active metabolites. The rest (5 % to 15 %) is excreted via the bile in the faeces. The non-metabolised drug substance is only found in traces (less than 1.0 %) in the urine.

Characteristics in Patients

Patients With Renal Impairment

There are no significant differences in the pharmacokinetics of nifedipine in patients with renal impairment and in healthy subjects. Therefore, dosage adjustments should not be required for patients with impaired renal function.

Patients With Hepatic Impairment

Nifedipine is primarily metabolised in the liver. The elimination half-life is markedly prolonged and there is a reduction in total clearance. Therefore, owing to the duration of action, nifedipine should not be administered to patients with reduced hepatic function.

5.3 Preclinical safety data

The LD_{50} values (in mg per Kg) determined when nifedipine was given orally and intravenously to different animal species, are reported below :

Animal Species	***Oral***	***Intravenous***
Mouse	454 (401 - 572) *	4.2 (3.8 - 4.6) *
Rat	1022 (950 - 1087) *	15.5 (13.7 - 17.5) *
Rabbit	250 - 500	2 - 3
Cat	~ 100	0.5 - 8
Dog	> 250	2 - 3

∗95 % confidence interval

Subacute & Subchronic Toxicity Studies (in Rats and Dogs)
Nifedipine doses of up to 50 mg per Kg in rats and 100 mg per Kg in dogs p.o were tolerated without any damage when administered orally over periods of thirteen and four weeks, respectively.

Nifedipine doses of 2.5 mg per Kg in rats and 0.1 mg per Kg in dogs were tolerated without any damage when administered intravenously over periods of three weeks and six days, respectively.

Chronic Toxicity Studies (in Rats and Dogs)
Nifedipine doses of up to and including 100 mg per Kg in dogs p.o were tolerated without any damage when administered orally up to one year.
In rats, toxic effect occurred at nifedipine concentrations above 100 ppm in the feed (about 5 mg to 7 mg per Kg body weight).

Carcinogenic Studies (in Rats)
Studies in rats over two years produced no evidence of carcinogenic effects caused by nifedipine.

Reproductive Studies (in Rats, Mice & Rabbits)
Studies in rats, mice and rabbits maternally toxic doses of nifedipine induced some teratogenic and embryotoxic effects.

Mutagenic Studies
In vivo and *in vitro* studies showed that nifedipine has no mutagenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In Tablet Core

Povidone K30
Lactose monohydrate
Carbomer 974P
Silica, colloidal anhydrous

In Tablet Core & Coat

Talc
Hypromellose (E. 464)
Magnesium stearate

In Tablet Coat

Dimethylaminoethyl methacrylate-Butyl methacrylate-Methyl methacrylate copolymer
Macrogol 4000
Red iron oxide (E. 172)
Titanium dioxide (E. 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf Life of the Medicinal Product as Packaged for Sale

24 months

Shelf Life After Dilution or Reconstitution

Not applicable

Shelf Life After First Opening the Container

Not applicable

6.4 Special precautions for storage

Do not store above 25 ºC. Keep blister in the outer carton.

6.5 Nature and contents of container

The tablets are enclosed in blisters composed of 25 µm aluminium foil coated with 20g.m^{-2} PVDC film / 250 µm PVC foil coated with 40g.m^{-2} PVDC film

The blisters are boxed in cardboard cartons containing 28 tablets and a patient information leaflet.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Chiesi Limited
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M22 5LG
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8. MARKETING AUTHORISATION NUMBER(S)

PL08829/0147

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

28th October 2004

10 DATE OF REVISION OF THE TEXT

24/05/2017