MODULE 1.3.1.1 PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME and dosage form

NIFEDIPINE CIPLA XR 30 Controlled release tablets.

NIFEDIPINE CIPLA XR 60 Controlled release tablets.

COMPOSITION

Each **NIFEDIPINE CIPLA XR 30** tablet contains 30 mg nifedipine.

Each **NIFEDIPINE CIPLA XR 60** tablet contains 60 mg nifedipine.

The inactive ingredients are cellulose acetate, ferric oxide, hydroxyl propyl methyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, sodium chloride, talc and titanium dioxide.

NIFEDIPINE CIPLA XR is sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 7.1 Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Nifedipine, a calcium antagonist, 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 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.

Pharmacokinetic properties:

NIFEDIPINE CIPLA XR tablets are formulated to release nifedipine at an approximately constant rate over 24 hours.

Absorption

Nifedipine is well and completely absorbed from the gastrointestinal tract after oral administration. However, due to extensive hepatic first pass metabolism in the liver, the resultant bioavailability is about 45 % to 60 %.

Distribution

Nifedipine is about 92 to 98 % bound to plasma proteins.

Metabolism

Nifedipine is extensively and rapidly metabolised in the liver with a prominent first-pass effect.

Elimination

About 80 % of the administered dose of nifedipine is excreted via the kidneys, mostly as its active metabolites. The rest (20 %) is excreted via the bile in the faeces.

INDICATIONS

NIFEDIPINE CIPLA XR is indicated for the:

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

CONTRA-INDICATIONS

Known hypersensitivity to nifedipine or any other ingredient of **NIFEDIPINE CIPLA XR**.

NIFEDIPINE CIPLA XR must not be used in patients with clinically significant aortic stenosis, in cardiogenic shock, unstable angina or within one month of a myocardial infarction.

Due to the duration of action of the formulation, **NIFEDIPINE CIPLA XR** should not be used in patients with hepatic impairment (see "**WARNINGS AND SPECIAL PRECAUTIONS**").

NIFEDIPINE CIPLA XR 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.

NIFEDIPINE CIPLA XR is contra-indicated in patients with inflammatory bowel disease.

NIFEDIPINE CIPLA XR should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction by rifampicin.

NIFEDIPINE CIPLA XR is contra-indicated in pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

Grapefruit juice inhibits the metabolism of **NIFEDIPINE CIPLA XR**. 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.

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 cases of severe aortic stenosis.

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, nefazodine, tacrolimus, carbamazepine, phenobarbitone and valproic acid. See **INTERACTIONS**.

NIFEDIPINE CIPLA XR is contra-indicated in pregnancy. However, care must be exercised in pregnant women when administering **NIFEDIPINE CIPLA XR** in combination with intravenous magnesium sulphate.

NIFEDIPINE CIPLA XR should not be switched once a patient has been stabilised. 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 cases of severe aortic stenosis.

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

NIFEDIPINE CIPLA XR should be used with caution in patients with a poor cardiac reserve.

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

Bezoars can occur and may require surgical intervention.

NIFEDIPINE CIPLA XR must not be used in patients with Kock pouch (ileostomy after proctocolectomy).

When doing barium contrast X-ray, **NIFEDIPINE CIPLA XR** 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* fertilisation, 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* fertilisation and if no other explanation can be found, nifedipine should be considered a possible reason.

Effects on ability to drive and use machines

Caution is advised for patients not to drive or use machines, until their individual susceptibility to the effects of **NIFEDIPINE CIPLA XR** is known.

INTERACTIONS

NIFEDIPINE CIPLA XR 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 induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of **NIFEDIPINE CIPLA XR**. The extent as well as the duration of interactions should be taken into account when administering **NIFEDIPINE CIPLA XR** together with the following medicines:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of **NIFEDIPINE CIPLA XR** is distinctly reduced and thus its efficacy weakened. The use of **NIFEDIPINE CIPLA XR** in combination with rifampicin is therefore contra-indicated (see "**CONTRAINDICATIONS**").

Erythromycin: Erythromycin is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore the potential for an increase of **NIFEDIPINE CIPLA XR** 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 **NIFEDIPINE CIPLA XR** and 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 **NIFEDIPINE CIPLA XR**. When administered together with **NIFEDIPINE CIPLA XR**, a substantial increase in plasma concentrations of **NIFEDIPINE CIPLA XR** 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 **NIFEDIPINE CIPLA XR** dose considered.

Ketoconazole, itraconazole, fluconazole: Medicines of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with **NIFEDIPINE CIPLA XR** a substantial increase in systemic bioavailability of **NIFEDIPINE CIPLA XR** 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 **NIFEDIPINE CIPLA XR** dose considered.

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

Nefazodone: A clinical study investigating the potential of an interaction between **NIFEDIPINE CIPLA XR** 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 **NIFEDIPINE CIPLA XR** plasma concentrations upon co-administration of both medicines cannot be excluded. When nefazodone is given together with **NIFEDIPINE CIPLA XR**, the blood pressure should be monitored and, if necessary, a reduction in the **NIFEDIPINE CIPLA XR** dose considered.

Quinupristin/Dalfopristin: Simultaneous administration of quinupristin/dalfopristin and **NIFEDIPINE CIPLA XR** may lead to increased plasma concentrations of **NIFEDIPINE CIPLA XR**. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the **NIFEDIPINE CIPLA XR** 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 **NIFEDIPINE CIPLA XR** plasma concentrations cannot be excluded.

Cimetidine: Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentration of **NIFEDIPINE CIPLA XR** and may potentiate the antihypertensive effect.

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

Phenytoin: Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of **NIFEDIPINE CIPLA XR** is reduced and thus its efficacy weakened. When both medicines are concomitantly administered, the clinical response of **NIFEDIPINE CIPLA XR** should be monitored and, if necessary, an increase of the **NIFEDIPINE CIPLA XR** dose considered. If the dose of **NIFEDIPINE CIPLA XR** is increased during co-administration of both medicines, a reduction of the **NIFEDIPINE CIPLA XR** dose should be considered when the treatment with phenytoin is discontinued.

Carbamazepine: As carbamazepine has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to

enzyme inhibition, an increase in **NIFEDIPINE CIPLA XR** plasma concentrations and hence an increase in efficacy cannot be excluded.

Phenobarbitone: As phenobarbitone has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in **NIFEDIPINE CIPLA XR** plasma concentrations and hence an increase in blood levels cannot be excluded.

Effects of **NIFEDIPINE CIPLA XR** on other medicines:

NIFEDIPINE CIPLA XR may increase the blood pressure lowering effect on concomitant applied antihypertensives, such as:

- Diuretics
- β-blockers
- ACE-inhibitors
- AT1-antogonists/Angiotensin 1 receptor blockers
- Other calcium antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa

When **NIFEDIPINE CIPLA XR** is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since severe hypotension can occur. Deterioration of heart failure is also known to develop.

Digoxin: The simultaneous administration of **NIFEDIPINE CIPLA XR** 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 toxicity as a

precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine: When **NIFEDIPINE CIPLA XR** and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of **NIFEDIPINE CIPLA XR**, a distinct increase in plasma concentrations of quinidine has been observed in individual cases. For this reason, when **NIFEDIPINE CIPLA XR** is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose is recommended. The blood pressure should be carefully monitored if quinidine is added to an existing therapy with **NIFEDIPINE CIPLA XR**. If necessary, the dose of **NIFEDIPINE CIPLA XR**, should be decreased.

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

Diltiazem: Diltiazem decreases the clearance of **NIFEDIPINE CIPLA XR**. **NIFEDIPINE CIPLA XR** 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.

Grapefruit juice: Grapefruit juice inhibits the metabolism of **NIFEDIPINE CIPLA XR**. Administration of **NIFEDIPINE CIPLA XR** together with grapefruit juice thus results in elevated plasma concentrations of **NIFEDIPINE CIPLA XR** due to a decreased first pass metabolism in the gastrointestinal tract. As a consequence, the blood pressure lowering effect may be increased.

Other forms of interactions:

NIFEDIPINE CIPLA XR may cause falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

PREGNANCY AND LACTATION

NIFEDIPINE CIPLA XR is contra-indicated in pregnant and lactating women (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

NIFEDIPINE CIPLA XR tablets should be swallowed whole with a glass of water and not bitten, broken up or chewed.

It is recommended that each dose of **NIFEDIPINE CIPLA XR** should be taken at approximately 24 hours intervals i.e. at the same time each day, preferably in the morning.

NIFEDIPINE CIPLA XR may be taken independently of mealtimes.

Adults: The recommended initial dose is one 30 mg tablet once daily. The dose may be increased according to individual requirements up to a maximum of 90 mg once daily. 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.

Patients with Renal Impairment: Dosage adjustments should not be required for patients with impaired renal function.

Elderly: A slight alteration of the pharmacokinetics of **NIFEDIPINE CIPLA XR** may be seen in the elderly. However, dosage adjustment in these patients is not usually necessary.

SIDE EFFECTS

The following adverse effects have been reported and are listed according to system organ class:

Immune system disorders:

Less frequent: Acute hypersensitivity reactions: Allergic reaction, allergic oedema/ angioedema (including larynx oedema); pruritus, urticaria, rash; anaphylactic reaction.

Psychiatric disorders:

Less frequent: Anxiety reactions, sleep disorders.

***Nervous system disorders*:**

Frequent: Headache.

Less frequent: Vertigo, migraine, dizziness, tremor, par-/dys-aesthesia.

Eye disorders:

Less frequent: Visual disturbance.

Cardiac disorders:

Less frequent: Tachycardia, palpitations.

Vascular disorders:

Frequent: Oedema, vasodilation.

Less frequent: Hypotension, syncope.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Nosebleed, nasal congestion, dyspnoea.

***Gastro-intestinal disorders*:**

Frequent: Constipation.

Less frequent: Gastro-intestinal and abdominal pain, dry mouth, dyspepsia, flatulence, vomiting, nausea, gingival hyperplasia, bezoar, dysphagia, intestinal obstruction, intestinal ulcer.

***Hepato-biliary disorders*:**

Less frequent: Transient increase in liver enzymes.

Skin and subcutaneous tissue disorders:

Less frequent: Erythema.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps, joint swelling.

Renal and urinary disorders:

Less frequent: Polyuria, dysuria.

Reproductive system disorders:

Less frequent: Erectile dysfunction.

General disorders and administration site conditions:

Frequent: Feeling unwell.

Less frequent: Unspecified pain, chills.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **SIDE EFFECTS**.

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 with added medicinal charcoal. If necessary in combination with irrigation of the small intestine.

Ipecacuanha should be given to children.

Haemodialysis serves no purpose, as **NIFEDIPINE CIPLA XR** is not dialyzable, but plasmapheresis is advisable. No specific antidote is available.

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

Hypotension as a result of cardiogenic shock and atrial vasodilation can 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 can 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 noradrenaline can additionally be administered. The dosage of these medicines is determined solely by the effect obtained.

Additionally liquid or volume must be administered with caution because of the danger of overloading the heart.

IDENTIFICATION

NIFEDIPINE CIPLA XR 30

Pink coloured, film-coated circular biconvex tablet having an orifice on one side and plain on the other.

NIFEDIPINE CIPLA XR 60

Pink coloured, film-coated circular biconvex tablet having an orifice on one side and plain on the other.

PRESENTATION

NIFEDIPINE CIPLA XR 30

Tablets are packed in plain aluminium and clear PVC/PE/PVdc blisters containing 14 tablets per blister placed in a carton

Pack size: 28's

NIFEDIPINE CIPLA XR 60

Tablets are packed in plain aluminium and clear PVC/PE/PVdc blisters containing 14 tablets per blister placed in a carton

Pack size: 28's.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not remove the blisters from the cartons until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

NIFEDIPINE CIPLA XR 30: 50/7.1/0619

NIFEDIPINE CIPLA XR 60: 50/7.1/0620

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

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