PACKAGE INSERT FOR

CIPALAT RETARD TABLETS

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

CIPALAT RETARD Tablets.

COMPOSITION:

Each tablet contains 20 mg nifedipine.

Inactive ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, polysorbate 80, povidone, magnesium stearate and colloidal silicon.

Film coating ingredients are hypromellose, ferric oxide red, purified talc and propylene glycol.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Nifedipine is a calcium antagonist which inhibits excitation-contraction coupling in myocardial and smooth muscle by blocking the transmembrane carrier of calcium. This results in vasodilatation as well as decreased myocardial contractility and myocardial oxygen demand. Nifedipine is also reported to act by reducing peripheral resistance. After oral administration of nifedipine, peripheral blood flow increases due to a decrease in sympathetic reflexes. **CIPALAT RETARD** displays controlled release characteristics.

Pharmacokinetic properties:

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract, but undergoes extensive hepatic first-pass metabolism, resulting in a bioavailability after oral administration of 45 to 75 %. Following administration by mouth, peak blood concentrations (T_{max}) occur at 5 – 6 hours with a half-life of 2 to 4 hours. Nifedipine is about 92 to 98 % bound to plasma proteins. It is extensively metabolised in the liver and 70 to 80 % of a dose is excreted in the urine almost entirely as the inactive metabolites. The absorption of nifedipine may be reduced by administration of food (see "**INTERACTIONS**").

INDICATIONS:

CIPALAT RETARD tablets are indicated for the prophylaxis of chronic stable angina pectoris, and also for the treatment of mild to moderate hypertension.

CONTRAINDICATIONS:

The use of **CIPALAT RETARD** during pregnancy and lactation is contra-indicated. (See "**PREGNANCY and LACTATION**")

Nifedipine is reported to be teratogenic in animals. It should not be used in patients who are hypersensitive to nifedipine or who are in cardiovascular shock.

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 event of severe aortic stenosis.

Nifedipine should not be used in hepatic and renal function impairment.

Nifedipine should not be used with rifampicin as no efficient plasma levels of nifedipine may be obtained due to enzyme induction by rifampicin. (See "**INTERACTIONS**")

Nifedipine is considered unsafe in patients with acute porphyria because it has been associated with acute attacks.

Nifedipine should not be administered to patients with hepatic impairment. Nifedipine should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract. Nifedipine is contra-indicated in patients with inflammatory bowel disease. Not recommended for use in children.

WARNINGS and SPECIAL PRECAUTIONS:

Nifedipine should be discontinued in patients who experience pain following its administration.

Grapefruit juice inhibits the metabolism of **CIPALAT RETARD**. After regular intake of grapefruit juice blood pressure lowering effect may last for atleast 3 days after the last ingestion of grapefruit (See "**INTERACTONS**").

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

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

Caution should be exercised in dialysis patients with malignant hypertension and irreversible kidney failure with hypovolaemia as a marked fall in blood pressure may occur. In patients with impaired liver function, careful monitoring and in severe cases, a dose reduction may be necessary.

Nifedipine may modify insulin and glucose responses calling for some adjustments in antidiabetic therapy.

Also some studies have suggested that nifedipine may worsen proteinuria and renal dysfunction in diabetic patients with some degree of renal insufficiency.

Arthralgia and insomnia may occur. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy. Hyperglycaemia has also been observed.

In single cases obstructive symptoms have been described without known history of gastrointestinal disorders. Nifedipine must not be used in patients with Kock

pouch (ileostomy after proctocolectomy). When doing barium contrast X-Ray, nifedipine may cause false positive effects (eg. Filling defects interpreted as polyp).

Care must be exercised in pregnant women, when administering nifedipine in combination with i.v magnesium sulphate.

Effects on ability to drive and use other machines

The effect on the ability to drive or operate machinery depends on the intensity of the reaction towards **CIPILAT RETARD** which varies from individual to individual. This effect to impair the ability to drive or operate machinery applies particularly at the start of treatment, on changing medication and in combination with alcohol.

INTERACTIONS:

Nifedipine is extensively metabolized in the liver by the cytochrome P450 enzyme system, and interactions, may occur with other medicines, such as quinidine, sharing the same metabolic pathway and enzyme inducers, such as carbamazepine, phenytoin, and rifampicin, and enzyme inhibitors, such as cimetidine and erythromycin.

The information concerning interactions with calcium channel blockers is still limited therefore some of the interactions listed below are included on a precautionary basis.

Medicine that affect nifedipine:

Nifedipine 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 nifedipine.

The extent of the duration as well as of interactions should be taken into account when nifedipine is administered together with the following medicines:

Rifampicin:

Nifedipine should not be used with rifampicin as no efficient plasma levels of nifedipine may be obtained due to enzyme induction by rifampicin. (See "**CONTRA-INDICATIONS**").

Non-steroidal anti-inflammatory drugs

Especially indomethacin may antagonize the antihypersensitive effect of calcium channel blocker, monitoring recommended.

Upon co-administration of known inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.

Medicine increasing nifedipine exposure:

Anaesthetics (inhalation hydrocarbons)

Together with calcium channel blockers may cause an additive hypotension.

Erythromycin:

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

Amprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir

A clinical study investigating the potential of a drug interaction between **CIPALAT RETARD** and indinavir, nelfinavir 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 **CIPALAT RETARD.** When administered together with **CIPALAT RETARD,** a substantial increase in plasma concentrations of **CIPALAT RETARD** due to decreased first pass metabolism and decreased elimination cannot be excluded. Upon co-administration, the blood pressure should be monitored and, if necessary, a reduction in the **CIPALAT RETARD** dose is considered.

Ketoconazole, Itraconazole, Fluconazole

Medicines in this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with **CIPALAT RETARD**, a substantial increase in systemic bioavailability of **CIPALAT RETARD** 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 **CIPALAT RETARD** dose is considered.

Fluoxetine

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

Nefazodone

A clinical study investigating the potential of a drug interaction between **CIPALAT RETARD** and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicine. Therefore an increase of **CIPALAT RETARD** plasma concentration of both medicines cannot be excluded. When nefazodone is given together with **CIPALAT RETARD**, the blood pressure should be monitored and, if necessary, a reduction in the **CIPALAT RETARD** dose considered.

Quinupristin/Dalfopristin

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

Valproic Acid

As valproic acid has been shown to increase the plasma concentration of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, and increase in **CIPALAT RETARD** plasma concentrations and hence an increase in efficacy cannot be excluded.

Cimetidine

Concurrent use may result in accumulation of calcium channel blockers as a result of inhibition of first-pass metabolism; caution and careful titration of nifedipine dose is recommended on starting the therapy in patients taking Cimetidine. Ranitidine and famotidine do not appear to significantly affect calcium channel blocker metabolism.

Cisapride

Simultaneous administration of cisapride and **CIPALAT RETARD** may lead to increased plasma concentrations of **CIPALAT RETARD.** Upon co-administration

of both medicines, the blood pressure should be monitored and if necessary, a reduction of the **CIPALAT RETARD** dose considered.

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nefidipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nefidipine is increased during co-administration of both medicines, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Medicines decreasing nifedipine exposure:

Alcohol

The metabolism of nifedipine is inhibited by alcohol and a maximum pulse rate was achieved more rapidly.

Calcium supplements

Concurrent use in sufficient quantities to elevate the calcium concentrations above normal may reduce the response to calcium channel blockers.

Phenytoin

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of **CIPALAT RETARD** is reduced and thus its efficacy weakened. When both mecidicines are concomitantly administered, the

clinical response to **CIPALAT RETARD** should be monitored and if necessary, and increase of the **CIPALAT RETARD** dose considered. If dose of **CIPALAT RETARD** is increased during co-administration of both medicines, a reduction of the **CIPALAT RETARD** dose should be considered when treatment with phenytoin is discontinued.

Carbamazepine

As carbamazepine has been shown to reduce the plasma concentration of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in **CIPALAT RETARD** plasma concentration 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 nomodipine due to enzyme induction, a decrease in **CIPALAT RETARD** plasma concentrations and hence a decrease in efficacy cannot be excluded.

Effects of nifedipine on other medicines:

CIPALAT RETARD may increase the blood pressure lowering effect on concomitant applied antihypertensives, such as:

- diuretics
- β-blockers

- ACE-inhibitors
- AT-antagonists/Angiotensin 1 receptor blockers
- other calcium antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa.

Beta-blockers (oral or othalmic)

The antihypertensive effect may be enhanced and therefore monitoring is recommended, when nifedipine is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Non-steroidal anti-inflammatory drugs

Especially indomethacin may antagonize the antihypersensitive effect of calcium channel blocker, monitoring recommended.

Hypotension-producing medications

Antihypertensive effects may be potentiated when these are used simultaneously with hypotension-producing calcium channel blockers.

Sympathomimetics

Concurrent use may reduce the antihypertensive effects of the calcium channel blockers; the patient should be carefully monitored.

Diltiazem

Decreases the clearance of nifedipine. **CIPALAT RETARD** 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.

Digoxin

Concurrent use with nifedipine has been reported to increase the serum concentrations of digoxin. Digoxin serum levels should be monitored and dosage adjusted if necessary when nifedipine therapy is initiated, changed or discontinued.

Disopyramide

Caution is recommended when Nifedipine is used concurrently with disopyramide.

Oestrogens

Oestrogen-induced fluid retention tends to increase the blood pressure, the patient should be carefully monitored if receiving concurrent therapy with calcium channel blockers.

Highly protein-bound medications

(Anticoagulants-coumarin and indandione, anticonvulsants-hydrantoin, quinine, salicylates, sulfinpyrazone) – caution is advised since changes in serum concentrations of the free, unbound medications may occur.

Quinidine

When **CIPALAT RETARD** and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of **CIPALAT RETARD**, a distinct increase in plasma concentrations of quinidine has been observed in individual cases. For this reason, when **CIPALAT RETARD** is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and if necessary, adjustment of the quinidine dose is recommended.

Some authors reported increased plasma concentrations of **CIPALAT RETARD** upon co-administration of both medicines, while others did not observe an alteration in the pharmacokinetics of **CIPALAT RETARD.** Therefore the blood pressure should be carefully monitored if quinidine is added to an existing therapy with **CIPALAT RETARD.** If necessary, the dose should be decreased.

Tacrolimus

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Upon co-administration of tacrolimus and **CIPALAT RETARD**, the

tacrolimus plasma concentration should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Food interactions

Grapefruit Juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of **CIPALAT RETARD** together with grapefruit juice thus results in elevated plasma concentrations of **CIPALAT RETARD** due to decreased first pass metabolism. As a consequence the blood pressure lowering effect of **CIPALAT RETARD** may be increased. This effect may last for at least three days after regular intake of grapefruit juice. (see "**WARNING** and **SPECIAL PRECAUTIONS**")

PREGNANCY AND LACTATION

Pregnancy

CIPALAT RETARD is contra-indicated in pregnancy before week 20. **CIPALAT RETARD** should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine.

From a 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.

Lactation

Nifedipine is excreted in 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.

It is not recommended to use **CIPALAT RETARD** during breast feeding, the effects of Nifedipine exposure to the infant are not known.

Fertility

In single cases of *in vitro* fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilisation, and where no other explanation can be found, calcium antagonists like nefidipine should be considered as possible causes.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose for **CIPALAT RETARD** is 20 to 40 mg twice per day.

The dosage interval is about 12 hours and should not be less than 2 – 4 hours.

Blood pressure should be monitored during initiation and upward titration of **CIPALAT RETARD**, especially if patients are on antihypertensive therapy.

The tablets should be taken with fluid before meals.

SIDE-EFFECTS

The most frequent side-effects are those associated with the vasodilator action of nifedipine: headache, flushing, dizziness, hypotension and peripheral oedema. Other events which may occur are dyspnoea, polyuria, weakness, nausea, a feeling of warmth, tiredness and other gastro-intestinal disturbances, increased micturition frequency, lethargy, eye pain, blurred vision and mental depression.

Skin reactions such as pruritus, urticaria, exanthema and in isolated cases exfoliative dermatitis have been observed. Unilateral gynaecomastia has been reported developing in men some weeks after starting nifedipine therapy.

Nifedipine may enhance or supplement the action of blood pressure lowering preparations. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness. In such cases a reduction in dosage or discontinuation of **CIPALAT RETARD** is recommended. Sudden withdrawal of nifedipine might be associated with an exacerbation of angina. Myocardial infarction has been reported.

Syncope has been reported but a recurrence can be prevented by a reduction in the dose of nifedipine. Tachycardia, palpitations – unrelated to congestive

cardiac failure- perspiration and nervousness have been reported. An increased frequency of angina may occur.

There have been reports of rashes, fever and abnormalities in liver function due to hypersensitivity reactions. Gingival hyperplasia has been reported but is often reversible on drug withdrawal.

Blood and lymphatic system disorders

Frequency unknown: Agranulocytosis and leucopenia

Immune system disorders

Less frequent: Allergic reaction, allergic oedema/angioedema (incl.larynx oedema), pruritus, urticaria and rash.

Frequency unknown: Anaphylactic/anaphylactoid reaction.

Psychiatric Disorders

Less frequent: Anxiety reactions and sleep disorders

Nervous System Disorders

Frequent: Headaches

Less frequent: Vertigo, migraine, dizziness, tremor and par/dysaesthesia.

Frequency unknown: Hypoaesthesia and somnolence

Eye Disorder

Less frequent: Visual disturbances

Frequency unknown: Eye pain

Cardiac disorders

Less frequent: Tachycardia, palpitations

Frequency unknown: Chest pain (Angina pectoris)

Vascular Disorders

Frequent: Oedema (Incl. peripheral oedema) and vasodilation.

Less frequent: Hypotension and Syncope

Respiratory, Thoracic and Mediastinal Disorders

Less frequent: Nosebleed and Nasal congestion

Frequency Unknown: Dyspnoea

Gastrointestinal disorders

Frequent: Constipation

Less frequent: Gastrointestinal and abdominal pain, nausea, dyspesia, flatulence, vomiting, dry mouth, and gingival hyperplasia.

Frequency unknown: Bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting and gastroesophageal sphincter insufficiency.

Hepatobiliary disorders

Less Frequent: Transient increase in liver enzymes

Frequency unknown: Jaundice

Skin and subcutaneous tissue disorders

Less frequent: Erythema

Frequency Unknown: Toxic Epidermal necrolysis, photosensitivity allergic reaction and palpable purpura.

Musculoskeletal and connective tissue disorders

Less Frequent: Muscle cramps and joint swelling

Frequency unknown: Arthralgia and Myalgia

Renal and urinary disorders

Less frequent: Polyuria and dysuria

Reproductive system and breast disorders

Less frequent: Erectile dysfunction

General disorders and administration site conditions

Less frequent: Feeling unwell, unspecific pain and chills.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Flushing, headaches, lowering of blood pressure, tachycardia or bardycardia, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, disturbances of consciousness to the point of coma. No specific antidote is available. Treatment is symptomatic and supportive.

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. Ipecacuanha should be given to children.

Haemodyalisis serves no purpose, as **CIPALAT RETARD** is not dialyzable, but plasmapheresis is advisable. Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympthomimetics, and in life-threatening bradycardiac disturbances of heart rhythm, temporary peacemaker therapy is advisable.

Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 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 sypathomimetics such as dopamine or noradrenaline can additionally be administered. The dosage of these medicines is determined solely by the effect obtained.

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

IDENTIFICATION:

Brown, circular, biconvex film-coated tablets.

PRESENTATION:

Cipalat Retard Tablets are available in blister packs of 60 and 120 tablets (strips of 10 tablets).

STORAGE INSTRUCTIONS:

Store below 30°C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

32/7.1.4/0660

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