NIFEDIPINE
ODIPIN

30 mg Extended-Release Tablet
CALCIUM CHANNEL BLOCKER

Rx

FORMULATION:
Each Extended-Release tablet contains:
Nifedipine, USP ..... 30 mg

PRODUCT DESCRIPTION:
Nifedipine is dihydropyridine calcium channel blocker. Its main uses are as an antianginal (especially in Prinzmetal's angina) and antihypertensive, although a large number of other indications have recently been found for this agent, such as Raynaud's phenomenon, premature labor, and painful spasms of pulmonary hypertension, patients whose symptoms respond to calcium channel blocker.

PHARMACOKINETICS:
General characteristics:
Nifedipine Extended-Release 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. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0-24 hour plasma concentration versus time profiles at steady state are plateau-like, rendering the Nifedipine Extended-Release Tablet appropriate for once-a-day administration.
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 form.

Absorption
Orally administered Nifedipine is almost completely absorbed in the gastrointestinal tract. The systemic availability of orally administered Nifedipine immediate release formulations (nifedipine capsules) is 45-56% owing to a first pass effect. At steady-state, the bioavailability of Nifedipine-Extended-Release Tablets ranges from 68-86% relative to Nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug 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 metabolized in the GUT wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5-15% being excreted via the bile in the faeces. Non-metabolized nifedipine can be detected only in traces (below 1.0%) 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 following Nifedipine-Extended-Release Tablets administration does represent a meaningful parameter as a plateau–like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of the last dose the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

Characteristics in patients:
There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.
In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. Owing to the duration of action of the formulation, Nifedipine Extended-Release Tablets should not be administered in these patients.

INDICATIONS:
For the treatment of all grades of hypertension.
For the prophylaxis of chronic stable angina pectoris either as mono therapy or in combination with a beta-blocker.

DOSAGE AND ADMINISTRATION:
Method and 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. Nifedipine Extended-Release Tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.
Nifedipine Extended-Release Tablet should not be taken with grapefruit juice.

Dosage regimen
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.
Patients in whom hypertension or angina symptoms are controlled on other nifedipine containing preparations may be safely switched to Nifedipine Extended-Release Tablets. Prophylactic anti-anginal efficacy is maintained when patients are switched from other calcium antagonists such as diltiazem or verapamil to Nifedipine Extended-Release Tablet. Patients switched from other calcium antagonists should initiate therapy at the recommended initial dose of 30 mg Nifedipine Extended-Release Tablets 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.

Duration of treatment
Treatment may be continued indefinitely.

Additional information on special populations
Children and adolescents
The safety and efficacy of Nifedipine Extended-Release Tablet in children below 18 years has not been established.
Elderly (>65 years)
Based on pharmacokinetic data on Nifedipine Extended-Release Tablet no dose adaption in elderly people above 65 years is necessary.
Patient with renal impairment
Based on the pharmacokinetic data, no dosage adjustment is required in patients with renal impairment.

CONTRAINDICATION:
Nifedipine Extended-Release Tablet should not be administered to patients with known hypersensitivity to nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
Nifidipine Extended-Release Tablet should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.
The safety of Nifedipine Extended-Release Tablet in malignant hypertension has not been established.
Nifedipine Extended-Release Tablet should not be used for secondary prevention of myocardial infarction.
Owing to the duration of action of the formulation, Nifedipine Extended-Release Tablet should not be administered to patients with hepatic impairment.
Nifedipine Extended-Release Tablet should not be administered to patients with a history of gastrointestinal obstruction, esophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract.
Nifedipine Extended-Release Tablet is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.
Nifedipine Extended-Release Tablet should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Nifedipine Extended-Release Tablet 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 risk must be exercised in patients with very low blood pressure (severe hypotension with systolic blood pressure less than 90 mm Hg)
Careful monitoring of blood pressure must be exercised with administering nifedipine with LV, magnesium sulphate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and fetus.
Nifedipine Extended-Release Tablet is not recommended for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known.
In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Nifedipine Extended-Release Tablet 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 Extended-Release Tablet will not prevent possible rebound effects after cessation of other antihypertensive therapy.
Nifedipine Extended-Release Tablet 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 Nifedipine Extended-Release may require adjustment of their control.
In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure may occur.
Nifedipine is metabolized 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.
Drugs, which are known inhibitors of 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 (e.g. ritonavir)
- Azole antimycotics (e.g. ketoconazole)
- Antidepressants, nefazodone and fluoxetine
- Quinupristine/dalfopristin
- Valproic acid
- Cimetidine

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy

Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity.

There are no adequate well controlled studies in pregnant women.

From the clinical evidence available a specific perinatal risk has not been identified, although an increase 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 after week 20 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.

Breastfeeding

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 breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant.

Fertility

In single cases of in vitro fertilization 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 fertilization, and no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Drugs that affect nifedipine:

Nifedipine is metabolized via the cytochrome P450 3A4 system, located both in the intestinal mucosa and liver. Drugs 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 as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus the efficacy weakened. The use of nifedipine is therefore contraindicated.

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. In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and drug(s) have been undertaken, thus far.

Drugs increasing nifedipine exposure:

- Marcrolide antibiotics (e.g. erythromycin)
- Anti-HIV protease inhibitors (retinonavir)
- Azole antimycotics (e.g. ketoconazole)
- Fluoxetine
- Nefazodone
- Qiunupristin/dalfopristin
- Cisapride
- Valproic acid
- Cimetidine
- Diltiazem

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

Drugs decreasing nifedipine exposure:

- Rifampicin (see above)
- Phenytoin
- Carbamazepine
- Phenobarbital

Effects of nifedipine on other drugs:

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives. When Nifedipine is administered simultaneously with β-receptor blocker the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin:

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin over dosage and, if necessary, the glycoside dose should be reduced.

Quinidine:

Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus:

Tacrolimus is metabolized via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in tacrolimus dose considered.

Drug food interactions

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due a decrease first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice. Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine.

Other forms of interaction

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

ADVERSE EFFECTS:

Blood and Lymphatic System Disorders: agranulocytosis, leucopenia

Immune System Disorders: allergic reaction, allergic oedema/angioedema (incl. larynx oedema), pruritus, urticarial rash, anaphylactic/anaphylactoid reaction.

Psychiactric Disorders: anxiety reactions, sleep disorders

Nervous System Disorders: headache, vertigo, migraine, dizziness, tremor, par-/dysesthesia

Eye Disorders: visual disturbances, hyperglycemia

Cardiac Disorders: tachycardia, palpitations, hypoaesthesia, somnolence

Vascular Disorders: oedema (incl. peripheral oedema), vasodilation, hypotension, syncope, eyepain.

Respiratory, Thoracic, and Mediastinal Disorders: nosebleed, nasal congestion, chest pains (angina pectoris)

Gastrointestinal Disorders: constipation, gastrointestinal and abdominal pain, nausea, dyspepsia, flatulence, dry mouth, gingival hyperplasia

Hepatobiliary Disorders: transient increase in liver enzymes, dyspnea

Skin and Subcutaneous Tissue Disorders: erythema, bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting, gastroesophageal sphincter insufficiency

Musculoskeletal and Connective Tissue Disorders: muscle cramps, joint swelling, jaundice

Renal and Urinary Disorders: polyuria, dysuria, toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura

Reproductive System and Breast Disorders: erectile dysfunction, arthralgia, myalgia

General Disorders and Administration Site Conditions: feeling unwell, unspecific pain, chills.

OVERDOSAGE AND TREATMENT:

A number of persons have developed toxicity due to acute overdosage with nifedipine, either accidentally or intentionally, and via either oral or parenteral administration. The adverse effects include lethargy, bradycardia, marked hypotension and loss of consciousness. The drug may be quantitated in blood or plasma to confirm a diagnosis of poisoning in hospitalized patients or to assist in a medicolegal death investigation. Analytical methods usually involve gas or liquid chromatography and specimen concentrations are usually in the 100-1000 µg/L range.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING:

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph". Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:

Store at temperatures not exceeding 30ºC.

DATE OF FIRST AUTHORIZATION: 23 May 2017

REGISTRATION NUMBER: DR-XY45317

AVAILABILITY:

Alu/Alu Blister Pack x 10's (Box of 30 Tablets)

Manufactured by:
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Manufactured for:
PRIMERA PHARMA CORP.
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