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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

PACKAGE INSERT

Nicardia XL 30

Nifedipine Extended Release Tablets USP 30 mg

Name and Strength of Active Ingredient (s)
Nifedipine (30 mg)

Product Description
Brown colored, round biconvex tablet, plain on one side and laser drilled hole on other side

Pharmacodynamics
Nifedipine is a specific and potent calcium antagonist of the 1, 4-dihydropyridine type. Calcium antagonists reduce the transmembrane influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. In hypertension, the main action of Nicardia XL 30 is to cause peripheral vasodilatation and thus reduce peripheral resistance. In angina, Nicardia XL 30 reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load. Additionally, nifedipine dilates submaximal both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium. Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis. Nicardia XL 30 administered twice-daily provides 24-hour control of raised blood pressure. Nicardia XL 30 causes reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Nicardia XL 30 has little or no effect on blood pressure.

Pharmocokinetics
Absorption
After oral administration nifedipine is rapidly and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 – 56 % owing to a first pass effect. Maximum plasma and serum concentrations are reached at 1.5 to 4.2 hours with Nicardia XL 30. Simultaneous food intake leads to delayed, but not reduced absorption.

Distribution
Nicardia XL 30 is about 95 % bound to plasma protein (albumin). The distribution half-life after intravenous administration was determined to be 5 to 6 minutes.

Biotransformation
After oral administration Nicardia XL 30 is metabolized in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nicardia XL 30 is excreted in the form of its metabolites predominantly via the kidneys and about 5 – 15 % via the bile in the faeces. The unchanged substance is recovered only in traces in the urine.

Elimination
The terminal elimination half-life is 6 - 11 hours, because of delayed absorption. In cases of impaired liver function the elimination half-life is distinctly prolonged and the total clearance is reduced. A dose reduction may be necessary in severe cases.

Indication
Nicardia XL 30 is a medicine for treatment of coronary heart disease; chronic stable angina pectoris (angina of effort). Treatment of hypertension.

Posology and Mode of administration
As far as possible the treatment must be tailored to the needs of the individual. Depending on the clinical picture in each case, the basic dose must be introduced gradually. Unless otherwise prescribed, the following dosage guidelines are recommended for adults:

For coronary heart disease: Chronic stable angina pectoris (angina of effort): Nicardia XL 30 tablet once daily (1 x 30 mg/day)

For hypertension: Nicardia XL 30 tablet once daily (1 x 30 mg/day).
In general therapy should be initiated with 30 mg once daily. Depending on the severity of the disease and the patient's response the dose can be increased in stages up to 120 mg once daily. 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 "Interaction with other medicinal products other forms of interaction").

Duration of Treatment: The attending doctor will determine the duration of use.

Administration: As a rule, Nicardia XL 30 tablet are swallowed whole with a little liquid, irrespective of meal times. Grapefruit juice is to be avoided (see "Interaction with other medicinal products and other forms of interaction").

Additional information on special populations:

Children and adolescents: The safety and efficacy of Nicardia XL 30 in children below 18 years has not been established.

Geriatric patients: Based on pharmacokinetic data for Nicardia XL 30 no dose adaptation in elderly people above 65 years is necessary.

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

Patients with renal impairment: Based on pharmacokinetic data no dosage adjustment is required in patients with renal impairment (see pharmacokinetic) The tablets must not be chewed or broken up.

Contraindication
Nicardia XL 30 must not be administered to patients with cardiovascular shock, with narrowing of the aorta (higher-grade aortic stenosis), with known hypersensitivity to Nicardia XL 30, with unstable angina pectoris and acute myocardial infarction (within the first 4 weeks).
Nicardia XL 30 should not be used to patients with extremely low blood pressure (severe hypotension with systolic blood pressure under 90mmHg) or existing (decompensated) heart muscle weakness.
Nicardia XL 30 should not be used for the treatment of acute attacks of angina.
Nicardia XL 30 should not be used for secondary prevention of myocardial infarction.
Nicardia XL 30 should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

Nicardia XL 30 should not be administrated to patients with hepatic impairment.
Nicardia XL 30 should not be administrated to patients with a history of gastro-intestinal obstruction, oesophageal obstruction or any degree of decreased lumen diameter of the gastro-intestinal tract.
Nicardia XL 30 must not be used in patients with a history of gastro-intestinal obstruction, oesophageal obstruction, any degree of decreased lumen diameters of the gastro-intestinal tract.
Nicardia XL 30 must not use in patient with a Kock pouch (ileostomy after Proctocolectomy).
Nicardia XL 30 is contra-indicated in patients with inflammatory bowel disease or Crohn's disease.

Warnings and Precautions
Nicardia XL 30 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).
In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.
Nicardia XL 30 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. Nicardia XL 30 will not prevent possible rebound effects after cessation of other antihypertensive therapy.
Nicardia XL 30 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 Nicardia XL 30 may require adjustment of their control as elevated blood glucose concentrations in serum (hyperglycaemia) upon taking.
Dialysis patients with severe, life-threatening high blood pressure (malignant hypertension) and irreversible kidney failure with reduced plasma volume (hypovolaemia) may experience particularly great blood pressure reduction through widening of blood vessels (vasodilation).
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.
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.

Treatment of high blood pressure with Nicardia XL 30 requires regular monitoring. Due to individually different reactions, alertness may be altered to such an extent that the ability to actively participate in road traffic or to operate machines or to work without a firm support is impaired. This applies especially at the start of treatment, when increasing the dose and when switching medicines as well as in combination with alcohol.

Interactions with other medicaments
Drugs that affect nifedipine
Nicardia XL 30 is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the 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 Nicardia XL 30.

The extent as well as the duration of interactions should be taken into account when administering Nicardia XL 30 together with the following drugs:

Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co- administration with rifampicin, the bioavailability of Nicardia XL 30 is distinctly reduced and thus its efficacy weakened. The use of Nicardia XL 30 in combination with rifampicin 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 Nicardia XL 30 dose considered. Drugs increasing Nicardia XL 30 exposure:

- Macrolide antibiotics (e.g., erythromycin)
- Anti-HIV protease inhibitors (e.g., ritonavir)
- Azole anti-mycotics (e.g., ketoconazole)
- Fluoxetine
- nefazodone
- quinupristin/dalfopristin
- cisapride
- valproic acid
- Cimetidine
- Diltiazem

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to Nicardia XL 30 should be monitored and, if necessary, an increase in the NICARDIA- XL-30 dose considered. If the dose of Nicardia XL 30 is increased during co-administration of both drugs, a reduction of the Nicardia XL 30 dose should be considered when the treatment is discontinued.

Drugs decreasing nifedipine exposure:
- rifampicin
- phenytoin
- carbamazepine
- phenobarbital

Effects of nifedipine on other drugs
Nicardia XL 30 may increase the blood pressure lowering effect of concomitant applied antihypertensives.

When Nicardia XL 30 is administered simultaneously with ß-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin: The simultaneous administration of Nicardia XL 30 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 overdosage and, if necessary, the glycoside dose should be reduced.

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Quinidine: Co-administration of Nicardia XL 30 with quinidine may lower plasma quinidine levels, and after discontinuation of Nicardia XL 30, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when Nicardia XL 30 is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose is recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with Nicardia XL 30 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 the tacrolimus dose considered.

Drug food interactions
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of Nicardia XL 30 together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of Nicardia XL 30 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 Nicardia XL 30.

Other forms of interaction
Taking Nicardia XL 30 may increase the spectrophotometric values of urinary vanillylmandelic acid, falsely. However, HPLC measurements are unaffected.

Pregnancy and Lactation
Pregnancy
Nicardia XL 30 should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nicardia XL 30 should be reserved for women with severe hypertension who are unresponsive to standard therapy.
Careful monitoring of blood pressure must be exercised when administering Nicardia XL 30 with I.V. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and foetus.

Lactation
Nicardia XL 30 is excreted in the breast milk. The Nicardia XL 30 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 Nicardia XL 30 exposure to the infant.

Undesirable Effects
The most common side effects are headache, reddening of the face (flushing) and sensation of heat. Other common side effects reported include:

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 disorder		
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 troctolitic during pregnancy

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

Overdose.
Symptoms
Overdosage or poisoning with NICARDIA-XL-30 may produce severe blood pressure fall, clouding of consciousness to the point of loss of consciousness, heart rhythm disturbances and breathlessness.

Treatment
As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. The benefit of gastric decontamination is uncertain.

a. Consider activated charcoal (50g for adults, 1g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

b. Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

c. Alternatively consider gastric lavage in adults within 1 hour of a potentially life- threatening overdose.

d. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulphate).

e. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution). Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10-20ml of a 10% calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required. Additional fluids should be administered with caution to avoid cardiac overload.

Storage Condition
Store below 30^{0}C. Protect from light and moisture. Keep out of reach of children.

Shelf Life
48 Months

Dosage Forms and Packaging available
Extended Release Tablets 30 mg
Alu- PVC Blister of 10 tablets. Three blisters are packed in a carton along with leaflet (3 x 10 Tablets).
Product complies with USP Dissolution Test-1

Manufactured by
UNIQUE PHARMACEUTICAL LABORATORIES
(A Div. of J. B. Chemicals and Pharmaceuticals Ltd.)
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Product Registration Holder and Imported By
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