Nifehexal® 20 Retard Tablet

Modified-release tablets

Content
Each modified-release tablet contains nifedipine 20mg.

Description
Pink to light red, round and biconvex tablets.

Properties
Nifedipine is a calcium-antagonist which inhibits the Ca^{2+} influx through the slow channels of vascular smooth muscle cell membrane. Since the intracellular calcium concentration plays a major role in the contraction of myocardial and vascular smooth muscle cells, inhibition of the entry of Ca^{2+} will reduce contractility and decrease vascular tone, resulting in vasodilatation. Nifedipine depresses cardiac contraction in the atrium, papillary, and trabecula muscles. By depressing cardiac contractions, nifedipine lessens cardiac workload with a consequent decrease in myocardial oxygen consumption.

After oral or sublingual administration of nifedipine, more than 90% of the administered drug is absorbed. Only 20% to 30% of nifedipine is removed from the portal blood by the liver, yielding a systemic bioavailability of more than 65%. The drug is detectable in the serum 3 minutes after sublingual administration and 20 minutes after oral administration. The peak blood concentration occurs 1 to 2 hours after oral use. The total duration of action is 8 to 12 hours. The main metabolic pathway consists of oxidation to a "free acid", a small fraction of which is converted to lactone. These metabolites are pharmacologically inert and do not accumulate in the body during long-term administration. Approximately 70 - 80% of the metabolised drug is eliminated via the kidney and 90% of the urinary excretion occurs during the first 24 hours.

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. Pediatric dosing forms are lacking.

Pharmacokinetics
The active substance nifedipine is rapidly and almost completely absorbed after oral intake on an empty stomach. Due to the first-pass-metabolism in the liver, systemic availability of orally administered nifedipine is 50 - 70%.

Maximum plasma or serum concentrations are achieved approximately 15 minutes after administration of a nifedipine-containing solution, and 30 to 85 minutes after administration of other preparations with non-retarded release.

Nifedipine is being linked to plasma protein (albumin) at a rate of 95 to 98%. A distribution volume (Vss) of 0.77 - 1.12 l/kg has been found for nifedipine.

Nifedipine is almost completely metabolised in the liver (high "first-pass-effect"), especially via oxidative processes. These metabolites do not show any pharmacodynamic activity.

Neither the unchanged substance, nor the metabolites M-1 are being eliminated renally at a significant rate (< 0.1 % of the dose). The polar metabolites M-2 and M-3 are found in the urine at a 50%-rate (partially in their conjugated state) while the major part is being excreted within 24 h. The rest is being excreted via the faeces.

The elimination half-life is 1.7 - 3.4 hours.

No accumulation of the substance has been described in long-term therapy with the usual dosage.

The elimination half-life is significantly prolonged, and the total clearance is reduced in patients with impaired hepatic function. Dose reduction may possibly be necessary.

Indications
1. For treatment of coronary heart disease, chronic stable angina pectoris (angina of effort).
2. For treatment of hypertension.

Adverse Reactions
The frequencies of ADRs reported with nifedipine containing products are summarised below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
Very common (≥1/10); Common (≥1/100 to <1/10>; Uncommon (≥1/1,000 to <1/100>; Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Not known: Agranulocytosis, leucopenia

Immune system disorders
Uncommon: Allergic reaction, allergic oedema/angioedema (incl. laryngeal oedema[1])
Rare: Pruritus, urticaria, rash
Not known: Anaphylactic/anaphylactoid reaction
[1] may result in life-threatening outcome

Psychiatric disorders
Uncommon: Anxiety reactions, sleep disorders

Metabolism and nutrition disorders
Not known: Hyperglycaemia

Nervous system disorders
Common: Headache
Uncommon: Vertigo, migraine, dizziness, tremor
Rare: Par-/Dysaesthesia
Not known: Hypoaesthesia, somnolence

Eye disorders
Uncommon: Visual disturbances
Not known: Eye pain

Cardiac disorders
Uncommon: Tachycardia, palpitations
Not known: Chest pain (Angina pectoris)
Very rare: Myocardial infarction

Vascular disorders
Common: Oedema, vasodilatation
Uncommon: Hypotension, syncope

Respiratory, thoracic and mediastinal disorders
Uncommon: Nosebleed, nasal congestion
Not known: Dyspnoea

Gastrointestinal disorders
Common: Constipation
Uncommon: Gastrointestinal and abdominal pain, nausea, dyspepsia, flatulence, dry mouth
Rare: Gingival hyperplasia
Not known: Bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting, gastroesophageal sphincter insufficiency

Hepatobiliary disorders
Uncommon: Transient increase in liver enzymes
Not known: Jaundice

Skin and subcutaneous tissue disorders
Uncommon: Erythema
Not known: Toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps, joint swelling

Not known: Arthralgia, myalgia

Renal and urinary disorders
Uncommon: Polyuria, dysuria

Pregnancy, puerperium and perinatal conditions
Unknown: Fetal distress syndrome

Reproductive system and breast disorders
Uncommon: Erectile dysfunction

General disorders and administration site reactions
Common: Feeling unwell, asthenia
Uncommon: Unspecific pain, chills

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

Precautions
In patients with essential hypertension or chronic angina pectoris treated with nifedipine in immediate-release pharmaceutical forms there was evidence of a dose-dependent increase in complications of the cardiovascular system (e.g. myocardial infarction) and increased mortality. For this reason, nifedipine is to be used in these diseases only if other medicinal products are not indicated.

Caution is necessary with dialysis patients who are suffering from malignant hypertension and irreversible kidney damage with hypovolaemia as a distinct fall in blood pressure can occur as a result of vasodilatation.

Nifedipine cannot be used to protect against the consequences of abrupt beta-blocker withdrawal. The use of nifedipine on diabetic patients may require adjustment of their glycaemic control. Abrupt withdrawal of nifedipine may precipitate rebound angina attacks.

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).

Care must be exercised in patients with manifest cardiac insufficiency.

Effects on ability to drive and use machines
Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

Contraindications
Nifehexal® 20 Retard must not be used in cases of: --
- hypersensitivity to nifedipine or to any of the other excipients
- cardiovascular shock
- clinically significant aortic stenosis
- unstable angina pectoris
- acute myocardial infarction (within the first 4 weeks)
- concurrent use with rifampicin (agent against tuberculosis)
- pregnancy before week 20 and during breastfeeding (see *Pregnancy and Lactation*)

Drug Interactions
Drugs that affect nifedipine:
Nifedipine 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 nifedipine. The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

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

Phenytoin, carbamazepine and phenobarbitone: Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of 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 with phenytoin is discontinued.

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy cannot be excluded.

Cytochrome P450 3A4 inhibitors
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.

Macrolide antibiotics: Certain macrolide antibiotics (e.g. erythromycin) are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded. Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors: A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors (e.g. amprenavir, indinavir, nelfinavir, ritonavir or saquinavir) has not yet been performed. Drugs of this class are known to inhibit the cytochromeP450 3A4 system. In addition, drugs of this class have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded.

Azole anti-mycotics: A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics (e.g. ketoconazole, itraconazole or fluconazole) has not yet been performed. Drugs of this class are known to inhibit the cytochrome P4503A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded.

Fluoxetine: A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded.

Nefazodone: A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded.

Quinupristin / Dalfopristin: Simultaneous administration of

quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine.

Valproic acid: No formal studies have been performed to investigate the potential interaction between nifedipine and 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 plasma concentrations and hence an increase in efficacy cannot be excluded.

Cimetidine: Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect.

Other drugs that affect nifedipine:
Cisapride: Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

Diltiazem: Diltiazem decreases the clearance of nifedipine and, hence, increases plasma nifedipine levels. Therefore, caution should be taken when both drugs are used in combination and a reduction of the nifedipine dose may be necessary.

Effects of nifedipine on other drugs:
Blood pressure lowering drugs: Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives, such as:
- diuretics
- β-blockers
- ACE-inhibitors
- AT-1 antagonists
- other calcium antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa

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.

Digoxin: The simultaneous administration of nifedipine 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 overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine: When nifedipine and quinidine have been administered simultaneously, lowered quinidine levels or, after discontinuation of nifedipine, a distinct increase in plasma concentrations of quinidine have been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose are recommended. Some authors reported increased plasma concentrations of nifedipine upon coadministration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine. Therefore, the blood pressure should be carefully monitored, if quinidine is added to an existing therapy with nifedipine. If necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus has been shown to be metabolised via the cytochrome P4503A4 system. Data recently published 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 the tacrolimus dose considered.

Vincristine: Nifedipine may reduce the excretion of vincristine. If necessary, a reduction in vincristine dose should therefore be taken into consideration.

Magnesium sulfate: The blood pressure has also to be carefully monitored when nifedipine is administered with i.v. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure which could harm both mother and fetus.

Cephalosporins: Concomitant administration of cephalosporins and nifedipine may increase the cephalosporin plasma levels.

Other forms of interaction:
Nifedipine may cause falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is unaffected.

Drug-food interactions:
Grapefruit juice
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 to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after the last ingestion of grapefruit juice. Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nifedipine.

Pregnancy and Lactation
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 where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

Pregnancy
Nifehexal® 20 Retard is contraindicated in pregnancy before week 20. In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity. There are no adequate and 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 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.

If **Nifehexal® 20 Retard** is used after the 20th week of pregnancy, this should be done only in a hospital with corresponding monitoring (blood pressure monitoring of the mother and continuous monitoring of fetal viability).

Lactation
Nifedipine passes into mother's milk. As no experience is available regarding possible effects on the infant, breastfeeding should be stopped if treatment with nifedipine is necessary during the lactation period.

Recommended dosage
Coronary heart disease, Chronic stable angina pectoris (angina of effort)
One **Nifehexal® 20 Retard** tablet twice daily. If a higher dosage is required, the dose can be increased in stages up to maximum 60mg daily.

Hypertension
One **Nifehexal® 20 Retard** tablet twice daily. If a higher dosage is required, the dose can be increased in stages up to maximum 60mg daily.

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

Elderly patients
The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Paediatric population
The safety and efficacy of nifedipine in children under the age 18 years have not been established.

Method and duration of administration
Nifehexal® 20 Retard is generally taken orally after meals, swallowed whole together with sufficient liquid, if possible at the same time each day, best in the morning and in the evening.

Concurrent intake of food leads to delay but not reduced absorption.

Nifedipine should be discontinued gradually, especially at high dosage.

The modified-release tablets should not be divided, as otherwise photoprotection achieved by the coating of the tablets cannot be guaranteed.

Symptoms and Treatment of Overdosage and Antidote
Symptoms
The following symptoms are observed in case of severe intoxication with nifedipine:
Depression of consciousness up to coma, fall in blood pressure, tachycardiac/bradycardiac arrhythmias, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Management of Overdose
As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority.

After oral ingestion thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine.

Particularly in cases of intoxication with slow-release products elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Bradycardiac heart rhythm disturbances may be treated symptomatically with ß-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.

Hypotension as a result of cardiogenic shock and arterial 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 range to slightly elevated levels. 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 is determined solely by the effect obtained.

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

Presentation:
Blister pack of 3 x 10, 5 x 10 and 10 x 10 tablets.

Do not store above 30°C.
Protect from light.
Jauhi daripada kanak-kanak.

Shelf life: Please refer to the outer box label.

Keep medicines out of reach of children

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Date of revision: Feb 2018