

# DATA SHEET

## NYEFAX RETARD

Nifedipine in a 20 mg film-coated tablet

### Presentation

Nifedipine USP in:

**20 mg Film-Coated Tablet:** Pale pink, biconvex, film-coated tablet of 7 mm diameter.

### Uses

#### *Actions*

#### Pharmacodynamic Properties

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal 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 the heart nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of the partially stenosed areas. Further, nifedipine reduces the vascular smooth muscle tone in the coronary arteries and prevents vasospasm. The final result is an increased poststenotic blood flow and an increased oxygen supply. Parallel to this, nifedipine reduces the oxygen requirement by lowering peripheral resistance (afterload). With long-term use nifedipine can also prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine reduces smooth muscle tone of the arterioles, thus lowering the increased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex increase in heart rate and thus in the cardiac output. However, this increase is not enough to compensate for the vasodilation. In addition, nifedipine increases sodium and water excretion both in the short-term and long-term use. The blood pressure lowering effect of nifedipine is particularly pronounced in hypertensive patients.

In Raynaud's syndrome nifedipine can prevent or reduce the digital vasospasm.

## ***Pharmacokinetics***

### **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 Nyefax Retard. Simultaneous food intake leads to delayed, but not reduced absorption.

The following table shows the peak plasma concentrations ( $C_{max}$ ) of Nyefax Retard and the corresponding times ( $t_{max}$ ):

<b>Dose</b>	<b><math>C_{max}</math> (mg/l)</b>	<b><math>t_{max}</math> (h)</b>
20 mg	26 - 77	1.5 – 4.2

### **Distribution:**

Nifedipine 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 nifedipine is metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity.

Nifedipine is excreted in the form of its metabolites predominantly via the kidney and about 5 – 15% via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1%) in the urine.

### **Elimination:**

The terminal elimination half-life is 6 – 11 hours because of delayed absorption. No accumulation of the substance after the usual dose was reported during long-term treatment.

In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers.

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.

## ***Indications***

Treatment of coronary heart disease

Chronic stable angina pectoris (angina of effort)

Treatment of hypertension.

## **Dosage and Administration**

### **Recommended usual dose:**

As far as possible the treatment must be tailored to the needs of the individual according to the severity of the disease and the patient's response.

Depending on the clinical picture in each case, the basic dose must be introduced gradually. In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Unless otherwise prescribed, the following dosage guidelines apply for adults:

### **In coronary heart disease:**

Chronic stable angina pectoris (angina of effort)      1 Nyefax Retard tablet twice daily  
(2 x 20 mg/day)

If higher dosages are necessary, the dose can be increased in stages up to a maximum of 60 mg daily.

### **In hypertension:**

1 Nyefax Retard tablet twice daily  
(2 x 20 mg/day)

If higher dosages are necessary, the dose can be increased in stages up to a maximum of 60 mg daily.

### **Duration of Treatment:**

The attending doctor will determine the duration of use.

Because Nyefax has a pronounced anti-ischaemic and anti-hypertensive action, it should be discontinued gradually, particularly when high doses are used.

### **Method of Administration:**

Tablets are generally swallowed whole with a little liquid, independently of meals. Simultaneous food intake leads to delayed but not reduced absorption.

The recommended dosage interval for Nyefax Retard is about 12 hours and should not be less than 4 hours.

## **Contraindications**

Nyefax must not be used in any formulation in cases of known hypersensitivity to nifedipine. Nifedipine must not be used during pregnancy and breastfeeding.

Nifedipine must not be used in cases of cardiovascular shock.

Nifedipine must not be used in combination with rifampicin because efficient plasma levels of nifedipine may not be obtained due to enzyme induction.

## **Warnings and Precautions**

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mmHg) in cases of manifest heart failure and in the cases of severe aortic stenosis.

Care must be exercised in pregnant women (See Contraindications), when administering nifedipine in combination with i.v. magnesium stearate.

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

## **Pregnancy and Lactation**

### ***Pregnancy***

Nifedipine is contraindicated throughout pregnancy.

Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies. Digital anomalies are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans.

There are no adequate and well-controlled studies in pregnant women.

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 nifedipine should be considered as possible causes.

### ***Breastfeeding***

Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

### ***Effect on Ability to Drive and Use Machines***

Reactions to the drug, which may 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.

## Adverse Effects

The most common adverse drug reactions described for nifedipine in clinical studies are listed as follows:

### Incidence of frequency $\geq 1\% < 10\%$

Body as a whole:	asthenia, oedema, headache
Cardiovascular system:	palpitation, peripheral oedema, vasodilation
Digestive system:	nausea
Nervous system:	dizziness

### Incidence of frequency $\geq 0.1\% < 1\%$

Body as a whole:	abdominal pain, chest pain, malaise, pain
Cardiovascular system:	angina pectoris, postural hypotension, syncope, tachycardia
Digestive system:	constipation, diarrhoea, dry mouth, dyspepsia, vomiting
Musculo-skeletal system:	arthralgia, myalgia
Nervous system:	Insomnia, nervousness, paraesthesia, somnolence, tremour, vertigo
Respiratory system:	dyspnoea
Skin and appendages:	pruritus, rash, skin disorder, sweating
Urogenital system:	nocturia, polyuria

### Incidence of frequency $\geq 0.01\% < 0.1\%$

Body as a whole:	abdomen enlargement, allergic reaction, photosensitivity reaction
Cardiovascular system:	hypotension
Digestive system:	flatulence, gastrointestinal disorder, GGTP increased, liver function test abnormal
Haemic and lymphatic system:	purpura
Nervous system:	hypesthesia
Skin and appendages:	urticaria
Special senses:	abnormal vision, amblyopia
Urogenital system:	urinary frequency increased

The most common adverse drug reactions based on spontaneous reports are listed below:

### Incidence of frequency $\geq 0.01\%$

Digestive system:	gum hyperplasia
Haemic and lymphatic system:	agranulocytosis
Skin and appendages:	gynaecomastia, erythromelalgia, exfoliative dermatitis
Other nifedipine formulations:	anaphylactic reaction

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

## **Interactions**

The blood pressure lowering effect of nifedipine may be potentiated by co-administration of other antihypertensive drugs.

When nifedipine is administered simultaneously with  $\beta$ -receptor blockers the patient should be carefully monitored, since fairly severe hypotension can occur. Deterioration of heart failure is also known to develop in isolated cases.

Nifedipine is metabolised via the cytochrome P450 3A4 system, located in both the intestinal mucosa and in the liver. Drugs 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.

### **Digoxin**

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin. As a precaution therefore, the patient should be checked for symptoms of digoxin overdosage, and in necessary, the dose should be reduced.

### **Phenytoin**

Phenytoin induces the cytochrome P450 3A4 system. With co-administration of phenytoin the bioavailability of nifedipine is reduced and 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 of phenytoin is discontinued.

### **Quinidine**

When nifedipine and quinidine have been administered simultaneously, occasionally lowered quinidine plasma concentrations have been observed. Also in some cases after the discontinuation of nifedipine a distinct increase in plasma concentrations of quinidine has been noted. 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.

### **Quinupristin/Dalfopristin**

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine. With co-administration of both drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose considered.

### **Cimetidine**

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the anti-hypertensive effect.

## **Rifampicin**

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

## **Diltiazem**

Diltiazem decreases the clearance of nifedipine. The combination of both drugs should be administered with caution and a reduction of the nifedipine dose may be considered.

## **Grapefruit Juice**

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice results in elevated plasma concentrations of nifedipine due to an increase of drug bioavailability. As a consequence, the blood pressure lowering effect may be increased.

## **Cisapride**

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. With co-administration of both drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

## **Theoretical Potential Interactions**

### **Erythromycin**

No interaction studies have been carried out between nifedipine and erythromycin. Erythromycin is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations with co-administration of erythromycin 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. When fluoxetine is given together with nifedipine, the blood pressure should be monitored, and if necessary, a reduction in the nifedipine dose considered.

### **Indinavir, Ritonavir, Saquinavir**

A clinical study investigating the potential drug interaction between nifedipine and indinavir, ritonavir or saquinavir has not yet been performed. Drugs 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. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to an increased absorption cannot be excluded. With co-administration, the

blood pressure should be monitored, and if necessary, a reduction in the nifedipine dose considered.

### **Ketoconazole, Itraconazole, Fluconazole**

A formal interaction study investigating the potential of a drug interaction between nifedipine and ketoconazole, itraconazole or fluconazole has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to an increased absorption cannot be excluded. With co-administration, the blood pressure should be monitored, and if necessary, a reduction in the nifedipine dose considered.

### **Tacrolimus**

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Data recently published indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. With co-administration the tacrolimus plasma concentrations should be monitored, and if necessary, a reduction in the tacrolimus dose considered.

### **Carbamazepine**

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine. As carbamazepine has 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.

### **Phenobarbitone**

No formal studies have been performed to investigate the potential interaction between nifedipine and phenobarbitone. As phenobarbitone has 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.

### **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 induction, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded.

### **Interactions Shown not to Exist**

Concomitant administration of the following drugs have been shown not to interfere with the pharmacokinetic properties of nifedipine:

- Ajmalin

- Benazepril
- Candesartan cilexetil
- Cerivastatin
- Debrisoquine
- Doxazosin
- Ibesartan
- Omeprazole
- Orlistat
- Pantoprazole
- Ranitidine
- Rosiglitazone
- Talinolol
- Triamterene hydrochlorothiazide

Concomitant administration of 100 mg aspirin with nifedipine has no effect on the pharmacokinetic properties of nifedipine. Co-administration of nifedipine does not alter the effect of aspirin 100 mg on the platelet aggregation and bleeding time.

#### **Other forms of interaction:**

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

### **Overdosage**

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac/bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

#### **Management of Overdose in Man**

As far as treatment is concerned, elimination of the active substance and 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 nifedipine formulations (such as Nyefax Retard) 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 dialyzable, but plasmapheresis is advisable (high plasma binding, relatively low volume of distribution).

Bradycardiac heart rhythm disturbances may be treated symptomatically with  $\beta$ -sympathomimetics, and in life-threatening bradycardiac disturbance 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 are additionally 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.

### **Pharmaceutical Precautions**

Protect from light and moisture. Store below 30°C. Keep out of reach of children.

### **Medicine Classification**

Prescription Medicine.

### **Package Quantities**

100 tablets.

30 tablets.

### **Further Information**

Nifedipine is 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridine dicarboxylic acid dimethyl ester. It has a molecular formula and weight of  $C_{16}H_{18}N_2O_6$  and 346.3 respectively.

Other ingredients of the tablets are: Microcrystalline cellulose, Maize cornflour, Lactose, Polysorbate 80 and Magnesium stearate.

### Preclinical Safety Data:

Acute toxicity has been investigated in various animal species and the individual results are listed in the following table:

	LD <sub>50</sub> (mg/kg)	
	oral	i.v.
Mouse	494 (421 – 572)*	4.2 (3.8 – 4.6)*
Rat	1022 (950 – 1087)*	15.5 (13.7 – 17.5)*
Rabbit	250 – 500	2 – 3
Cat	~ 100	0.5 – 8
Dog	> 250	2 - 3

\* 95% confidence interval

### Subacute and Subchronic Toxicity

Daily oral administration of rats (50 mg/kg body weight) and to dogs (100 mg/kg body weight) over periods of 13 and 4 weeks respectively were tolerated without toxic effects.

After parenteral (i.v.) administration dogs tolerated up to 0.1 mg/kg body weight/day for 6 days without damage. Daily i.v. administration of 2.5 mg/kg body weight in rats over a period of 3 weeks was also tolerated without signs of damage.

### Chronic Toxicity:

Dogs tolerated up to 100 mg/kg body weight as a daily oral dose over a period of 1 year without toxic damage. In rats toxic effects occurred at concentrations about 100 ppm in the feed (about 5-7 mg/kg body weight).

### Carcinogenicity:

A long-term study in rats (2 years) yielded no evidence of a carcinogenic effect of nifedipine.

### Reproduction Toxicology:

Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital abnormalities. Digital anomalies are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans.

### Mutagenicity:

To assess the mutagenic effects the Ames test, the Dominant-lethal test, and the Micronucleus test were performed in the mouse. No evidence of a mutagenic effect of nifedipine could be found.

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