New Zealand Data Sheet

1. PRODUCT NAME

Nyefax® Retard modified-release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 20 mg nifedipine.

Excipient(s) with known effect

Contains lactose monohydrate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablets.
Pale pink, biconvex, film-coated tablet of 7 mm diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of coronary heart disease
- Chronic stable angina pectoris (angina of effort)
- Treatment of hypertension

4.2. Dose and method of administration

Dose

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.

Adults

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.

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 (refer to section 4.5).

Duration of Treatment

The attending doctor will determine the duration of use.

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

Special Population

Use in elderly

The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine modified release tablet may be required comparted to younger patients.

Hepatic impairment

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (refer to sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of nifedipine modified release tablet in children below 18 years has not been established.

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.

4.3. Contraindications

Nyefax Retard 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.

4.4. Special warnings and precautions for use

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.

There are no safety and efficacy data from well-controlled studies in pregnant women (refer to section 4.6).

Animal studies have shown a variety of embryotoxic, placentotoxic and fetotoxic effects when administered during and after the period of organogenesis (refer to section 5.3).

From the clinical evidence available, a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean deliveries 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.

Care must be exercised in pregnant women (refer to section 4.3), when administering nifedipine in combination with i.v. magnesium sulfate, owing to the possibility of an excessive fall in blood pressure, which could harm both mother and fetus.

In patients with mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine have not been investigated in patients with severe hepatic impairment (refer to section 4.2 and 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (refer to section 4.5).

Medicines which are weak to moderate inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine, are, e, g.:

- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- azole antimycotics (e.g. ketoconazole)
- the antidepressants of nefazodone and fluoxetine
- quinupristin/ dalfopristin
- valproic acid
- cimetidine

Upon co-administration with these medicines, the blood pressure should be monitored and if necessary, a reduction of the nifedipine dose should be considered.

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For use in special populations (refer to section 4.2).

4.5. Interaction with other medicines and other forms of interaction

Medicines that affect nifedipine

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

When nifedipine is administered simultaneously with β-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. Medicines 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 (refer to section 4.4).

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

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.

Upon co-administration of following weak to moderate inhibitors of the cytochrome P540 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (refer to section 4.2).

Macrolide antibiotics (e.g. erythromycin)

No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, the potential for an increase of nifedipine plasma concentrations with coadministration of erythromycin cannot be excluded (refer to section 4.4).

Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP 3A4 inhibition.

Anti-HIV protease inhibitors (e.g. ritonavir)

A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Medicines of this class are known to inhibit the cytochrome P450 3A4 system. In addition, medicines 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 an increased absorption and decreased elimination cannot be excluded (refer to section 4.4).

Azole anti-mycotics (e.g. ketoconazole)

A formal interaction study investigating the potential of a drug interaction between nifedipine and azole anti-mycotics has not yet been performed. Medicines 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 (refer to section 4.4).

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 medicines cannot be excluded (refer to section 4.4).

Nefazodone

A clinical study investigating the potential of drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other medicines. Therefore, an increase of nifedipine plasma concentration upon co-administration of both drugs cannot be excluded (refer to section 4.4).

Quinupristin/Dalfopristin

Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (refer to section 4.4).

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 (refer to section 4.4).

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the anti-hypertensive effect (refer to section 4.4).

Further studies

Cisapride

Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

Anti-epileptic medicines

Cytochrome P450 3A4 system inducing anti-epileptic medicines, such as phenytoin, carbamazepine and phenobarbitone.

Phenytoin induces the cytochrome P450 3A4 system. With co-administration of phenytoin, the bioavailability of nifedipine is reduced and its efficacy weakened. When both medicines are concomitantly administrated, the clinical response to 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 medicines, 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 medicines 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.

Effects of nifedipine on other medicines

Blood pressure lowering medicines

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives, such as:

- diuretics

- β blockers
- ACE inhibitors
- angiotensin II receptor-antagonists
- other calcium antagonists
- α-adrenergic blocking agents
- PDE5 inhibitors
- α-methyldopa

When nifedipine is administrated 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. As a precaution therefore, the patient should be checked for symptoms of digoxin overdosage, and in necessary, the glycoside dose should be reduced, taking account of the plasma concentration of digoxin.

Quinidine

When nifedipine and quinidine have been administered simultaneously, occasionally lowered quinidine plasma concentrations have been observed in individual cases. Some authors reported increased plasma concentrations. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both medicines, 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. 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 is recommended.

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.

Drug-food interactions

Grapefruit Juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice 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 white taking nifedipine (refer to section 4.2).

Interactions Shown not to Exist

Ajmalin

Concomitant administration of nifedipine and ajmaline has no effect on the metabolism of ajmaline.

Aspirin

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

Benazepril

Concomitant administration of nifedipine and benazepril has no effect on the pharmacokinetics of nifedipine.

Candesartan cilexetil

Concomitant administration of nifedipine and candesartan/cilexetil has no effect on the pharmacokinetics of either medicine.

Debrisoquine

Concomitant administration of nifedipine and debrisoquine has no effect on the metabolic ratio of debrisoquine.

Doxazosin

Concomitant administration of nifedipine and doxazosin has no effect on the pharmacokinetics of nifedipine.

Irbesartan

Concomitant administration of nifedipine and irbesartan has no effect on the pharmacokinetics of irbesartan.

Omeprazole

Concomitant administration of nifedipine and omeprazole has no clinically relevant effect on the pharmacokinetics of nifedipine.

Orlistat

Concomitant administration of nifedipine and orlistat has no effect on the pharmacokinetics of nifedipine.

Pantoprazole

Concomitant administration of nifedipine and pantoprazole has no effect on the pharmacokinetics of nifedipine.

Ranitidine

Concomitant administration of nifedipine and ranitidine has no effect on the pharmacokinetics of nifedipine.

Rosiglitazone

Concomitant administration of nifedipine and rosiglitazone has no clinically relevant effect on the pharmacokinetics of nifedipine.

Talinolol

Concomitant administration of nifedipine and talinolol has no effect on the pharmacokinetics of nifedipine.

Triamterene hydrochlorothiazide

Concomitant administration of nifedipine and triamterene hydrochlorothiazide has no effect on the pharmacokinetics of nifedipine.

Other forms of interaction

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

4.6. Fertility, pregnancy and lactation

Pregnancy

Nifedipine is contraindicated in pregnancy before week 20. There are no adequate and well-controlled studies in pregnant women.

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal 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 fetotoxic effects in animals were maternally toxic at several times the recommended maximum dose for humans.

Breast-feeding

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.

Fertility

***In vitro* fertilisation**

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.

4.7. Effects 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.

4.8. Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2661; placebo n = 1486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3825; placebo n = 3840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

The frequencies of ADRs reported with nifedipine containing products are summarised in Table 1 below. With each frequency grouping, ADRs are presented in order of decreasing seriousness.

The frequencies are defined as:

Common ≥ 1/100 to < 1/10 (≥1% to <10%)
Uncommon ≥ 1/1000 to < 1/100 (≥0.1% to <1%)
Rare ≥ 1/10000 to < 1/1000 (≥0.01% to <0.1%)

Table 1 Adverse drug reactions reported on clinical trial data

System Organ Class	Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%
Immune system disorders		Allergic reaction Allergic oedema/angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash
Psychiatric disorders		Anxiety reactions Sleep disorders	
Nervous system disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/Dysaesthesia
Eye disorders		Visual disturbances	
Cardiac disorders		Tachycardia Palpitations	
Vascular disorders	Oedema Vasodilatation	Hypotension Syncope	
Respiratory, thoracic, and mediastinal disorders		Nasal congestion Nosebleed	
Gastrointestinal disorders	Constipation	Gastrointestinal Abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia
Hepatobiliary disorders		Transient increase in liver enzymes	
Skin and subcutaneous tissue disorders		Erythema	
Musculoskeletal and connective tissue disorders		Muscle cramps Joint swelling	
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

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

Post marketing adverse effects

The ADRs identified during the ongoing market surveillance and for which a frequency could not be estimated are: agranulocytosis, leukopaenia, anaphylactic/anaphylactoid reaction, hyperglycaemia, hypoaesthesia, somnolence, eye pain, chest pain (angina pectoris), dyspnoea, vomiting, gastrooesophageal sphincter insufficiency, jaundice, toxic epidermal necrolysis, photosensitivity allergic reaction, palpable purpura, arthralgia and myalgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms

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.

Treatment

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 dialysable, but plasmapheresis is advisable (high plasma binding, relatively low volume of distribution).

Bradycardiac heart rhythm disturbances may be treated symptomatically with β-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 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, ATC code: C08CA05

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 occurring digital vasospasm.

5.2. Pharmacokinetic properties

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 nifedipine. Simultaneous food intake leads to delayed, but not reduced absorption.

Table 2 Peak plasma concentrations and *the time to reach peak plasma concentrations*

Dose	C_{max} (mg/l)	T_{max} (h)
20 mg	26-74	1.6-4.2

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 a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result, AUC and Cmax of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine have not been investigated in patients with severe hepatic impairment (refer to section 4.4).

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Acute toxicity

Acute toxicity has been investigated in various animal species and the individual results are listed in table 3.

Table 3 Acute toxicity in various animal species

	LD_{50} (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

Sub-acute and Sub-chronic 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 above 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, mice and rabbits, including digital anomalies, malformation of extremities, cleft palates, cleft sternum and malformation of the ribs.

Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

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 (refer to section 4.6).

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Nyefax® Retard modified-release tablet contains iron oxide black, iron oxide red, lactose monohydrate, macrogol 4000, magnesium stearate, methylcellulose, microcrystalline cellulose, polysorbate 80, pregelatinised maize starch, purified water, titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Blister pack: Store at or below 30°C.
Bottle plastic: Store at or below 25°C.

Protect from light and moisture.

6.5. Nature and contents of container

Blister pack, 30 tablets
Bottle plastic, 100 tablets
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

20 February 1986

10. DATE OF REVISION OF THE TEXT

13 July 2023

Summary table of changes

Section Changed	Summary of new information
6.4	Changed storage conditions: Store at or below 25 °C, added “protect from light and moisture” to align with label.