PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNIFEDIPINE

Nifedipine Capsules

Capsules, 5 mg and 10 mg, Oral

USP

Anti-Anginal Agent

AA PHARMA INC.
1165 Creditstone Road Unit # 1
Vaughan, Ontario
L4K 4N7
www.aapharma.ca/en/

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RECENT MAJOR LABEL CHANGES

None	N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NIFEDIPINE (nifedipine capsules) is indicated for:

- Management of angina resulting from coronary artery spasm.
- Management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

NIFEDIPINE may be used in combination with beta blocking drugs in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy care must be taken to monitor blood pressure closely, since severe hypotension can occur from the combined effects of the drugs (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

NIFEDIPINE is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Patients with a known hypersensitivity to other dihydropyridines calcium antagonists, because of the theoretical risk of cross-reactivity.
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).
- Nursing women (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- Combination with rifampicin because effective plasma levels of nifedipine may not be achieved due to induction of the enzyme metabolizing nifedipine.
- Patients with acute myocardial infarction (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Patients with Myocardial Infarction).
- Patients with cardiovascular shock.
- Patients with severe hypotension.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage should be individualized depending on patient tolerance and response.

4.2 Recommended Dose and Dosage Adjustment

The starting dose of NIFEDIPINE is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective dose range is 10 to 20 mg three times daily. Some patients, especially those with evidence of coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, doses of 20 to 30 mg three or four times daily may be effective. A maximum daily dose of 120 mg should not be exceeded.

In general there should be an interval of at least three days between increases in dose in order to adequately assess the response to a particular dose level. In hospitalized patients under close observation the titration phase may proceed more rapidly.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Geriatrics

NIFEDIPINE should be administered cautiously to elderly patients and the dosage should be carefully and gradually adjusted depending on patient tolerance and response (see 7.1.4 Geriatrics).

Patients with Hepatic Impairment

In patients with impaired liver function, careful monitoring should be performed and a dose reduction may be necessary.

NIFEDIPINE 5 mg capsules provide for greater flexibility of dose titration, e.g. in elderly patients and patients with hepatic impairment.

4.4 Administration

NIFEDIPINE capsules must be swallowed whole.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the

regular dosing schedule. Do not take a double dose to make up for the forgotten dose.

5 OVERDOSAGE

There are several well documented cases of nifedipine immediate-release overdosage. The following symptoms are observed in cases of severe nifedipine intoxication: disturbance of consciousness to the point of coma, a drop in blood pressure, tachycardia/bradycardia, hyperglycemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary edema.

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

Clinically significant hypotension calls for active cardiovascular support including monitoring of cardiac and respiratory function including elevation of extremities and attention to circulating fluid volume and urine output.

Hypotension as a result of arterial vasodilation can also be treated with calcium (10 mL of 10% calcium gluconate solution administered slowly via intravenous route 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 as a last resort only in patients without cardiac arrhythmia or ischemic heart disease and when other safer measures have failed. 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.

Bradycardia and/or bradyarrhythmias have been observed in some cases of nifedipine overdosage. Appropriate clinical measures, according to the nature and severity of the symptoms, should be applied.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules 5 mg, 10 mg of nifedipine	Benzyl alcohol, FD&C yellow #6, gelatin, glycerin, iron oxide yellow, lemon oil, mannitol, polyethylene glycol, sorbitan sorbitol solution, titanium dioxide, and white ink.

NIFEDIPINE (nifedipine) 5 mg: each opaque, mustard colour, oval, soft gelatin capsule, imprinted '5' in white ink with clear, yellow liquid fill, contains nifedipine 5 mg. Available in bottles of 100.

NIFEDIPINE (nifedipine) 10 mg: each opaque, mustard colour, oblong, soft gelatin capsule, imprinted '10' with clear yellow liquid fill, contains nifedipine 10 mg. Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

General

Concomitant Use with Strong Inhibitors of CYP 3A4

Use of Nifedipine with drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of nifedipine and associated serious adverse events (see 9 DRUG INTERACTION). Such concomitant use should be avoided.

An observational study demonstrated an increased risk of hospitalization with acute kidney injury when nifedipine was used concomitantly with clarithromycin in elderly patients (>65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio [nifedipine: 5.33 (95% C.I. 3.39 – 8.38)].

Cardiovascular

NIFEDIPINE should be used with care in the following conditions:

Excessive Hypotension

Since NIFEDIPINE lowers peripheral vascular resistance and blood pressure, NIFEDIPINE should be used cautiously in patients who are prone to develop hypotension and those with a history of cerebrovascular insufficiency. Occasional patients have had excessive and poorly tolerated hypotension. Syncope has been reported (see 8.2 Clinical Trial Adverse Reactions, Cardiac disorders). These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers. If excessive hypotension occurs, dosage should be lowered or the drug should be discontinued (see 2 CONTRAINDICATIONS).

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Patients with Myocardial Infarction

NIFEDIPINE should not be used within one week after myocardial infarction and not before the patient has stabilized. Randomized, placebo-controlled clinical trials have indicated that nifedipine may increase the risk of reinfarction and worsen survival in patients treated early after myocardial infarction (see 2 CONTRAINDICATIONS).

Patients with Unstable Angina

Some clinical trials have shown that treatment with nifedipine in this setting increases the risk of myocardial infarction and recurrent ischemia.

Hypertension

NIFEDIPINE should not be used for the management of essential hypertension.

Acute Reduction of Blood Pressure

NIFEDIPINE should not be used for acute reduction of blood pressure. Strokes have occurred when nifedipine was used in this setting.

Beta Blocker Withdrawal

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and nifedipine initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine.

Patients with Heart Failure

There have been isolated reports of severe hypotension and lowering of cardiac output following administration of nifedipine to patients with severe heart failure. Thus, NIFEDIPINE should be used cautiously in patients with severe heart failure. Rarely, patients usually receiving

a beta blocker, have developed heart failure after beginning nifedipine therapy.

In patients with severe aortic stenosis, nifedipine will not produce its usual afterload-reducing effects, and there is a possibility that an unopposed negative inotropic action of the drug may produce heart failure if the end-diastolic pressure is raised. Caution should therefore be exercised when using NIFEDIPINE in patients with these conditions.

Peripheral Edema

Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, has been reported to occur in patients treated with nifedipine (see 8.2 Clinical Trial Adverse Reactions, Cardiac disorders). This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Driving and Operating Machinery

Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery, particularly at the start of the treatment, upon changing the medication, or in combination with alcohol. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Use in Diabetic Patients

The use of NIFEDIPINE in diabetic patients may require adjustment of their blood glucose control.

Hepatic/Biliary/Pancreatic

Use in Patients with Impaired Liver Function

NIFEDIPINE should be used with caution in patients with impaired liver function (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic insufficiency). A dose reduction, may be required. The response and metabolic effect should be monitored closely.

Monitoring and Laboratory Tests

Hypotension/Heart Rate

Because NIFEDIPINE is an arterial and arteriolar vasodilator, hypotension and a compensatory increase in heart rate may occur. Thus, blood pressure and heart rate should be monitored carefully during nifedipine therapy. Close monitoring is especially recommended for patients who are prone to develop hypotension, those with a history of cerebrovascular insufficiency, and those who are taking medications that are known to lower blood pressure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Reproductive Health: Female and Male Potential

Male Fertility

In some cases of in vitro fertilization, nifedipine has been associated with reversible spermatozoal biochemical changes. In vitro studies have shown that nifedipine may inhibit expression of mannose-ligand receptors, thus preventing the spermatozoa from attaching to the zona pellucida and impairing sperm function. In those men who are repeatedly unsuccessful in fathering a child by in vitro fertilization, and where no other explanation could be found, nifedipine should be considered as a possible cause.

Women of Child-bearing Potential/Contraception

NIFEDIPINE may cause embryo-fetal harm when administered during pregnancy. Women of child-bearing potential should use effective contraception during treatment with NIFEDIPINE (see 7.1.1 Pregnant Women and 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

NIFEDIPINE is contraindicated during pregnancy. Fetal malformations and adverse effects on pregnancy have been reported in animals. An increase in the number of fetal mortalities and resorptions occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice, rats and rabbits. Fetal malformations occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice and 100 mg/kg to pregnant rats (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

NIFEDIPINE is contraindicated in use during breast-feeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): NIFEDIPINE should be administered cautiously to elderly patients, especially to those with a history of hypotension or cerebral vascular insufficiency (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse effects, which generally result from the vasodilating effects of nifedipine were: headache (7.2%); dizziness, lightheadedness and giddiness (6.7%), nausea and

vomiting and gastrointestinal distress (6.7%); flushing and heat sensation (5.8%); peripheral edema (3.7%) and hypotension (2.0%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

A safety analysis from the world literature (controlled and open studies) was carried out in a heterogeneous group of 7146 patients who were treated with nifedipine. Adverse effects were reported in 27.9% of patients and required discontinuation of treatment in 5.5% of patients.

As a part of the above analysis, a more comprehensive safety evaluation (controlled and open studies) was carried out in 3074 patients, some of whom were severely ill and were receiving a variety of concomitant drugs, such as beta-blockers, nitrates, antiarrhythmics, cardiac glycosides, diuretics and anti-platelet drugs, etc.

The following adverse effects divided by systems were reported in these 3074 patients:

Cardiac disorders

Common (≥1% and <10%):

Peripheral edema:	8.3%
Palpitation and increased heart rate:	2.6%

Uncommon (≥0.1% and <1%):

Syncope:	0.4%

Rarely (≥0.01% and ≤1%), and possibly due to tachycardia, nifedipine has been reported to have precipitated an angina pectoris attack. In addition, more serious events were occasionally observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. These events include myocardial infarction, congestive heart failure or pulmonary edema, and ventricular arrhythmias or conduction disturbances.

Eye disorders

Uncommon (≥0.1% and <1%):

Blurred vision:	0.9%

Gastrointestinal disorders

Common (≥1% and <10%):

Nausea and vomiting:	6.4%
Abdominal discomfort and heartburn:	2.0%

Uncommon (≥0.1% and <1%):	
Diarrhea:	0.9%
Constipation:	0.6%
General disorders and administration site conditions	
Common (≥1% and <10%):	
Swelling:	8.3%
Heat sensation:	7.4%
General weakness:	6.3%
Jitteriness:	1.9%
Fever, sweating and chills:	1.4%
Metabolism and nutrition disorders	
Common (≥1% and <10%):	
Fluid retention:	8.3%
Musculoskeletal and connective tissue disorders	
Common (≥1% and <10%):	
Joint stiffness, muscle pain and cramps:	4.3%
Nervous system disorders	
Very common (≥10%):	
Dizziness, lightheadedness, giddiness:	11.9%
Common (≥1% and <10%):	
Headache:	7.8%
Shakiness, nervousness:	1.9%
Sleep disturbances:	1.1%
Psychiatric disorders	
Uncommon (≥0.1% and <1%):	
Depression:	0.6%
Respiratory, thoracic and mediastinal disorders	
Common (≥1% and <10%):	
Shortness of breath, dyspnea:	1.3%
Uncommon (≥0.1% and <1%):	
Nasal congestion:	0.5%

Skin and subcutaneous tissue disorders

Common (≥1% and <10%):

Pruritus, dermatitis, urticaria and rash:	1.9%

Vascular disorders:

Common (≥1% and <10%):

Flushing:	7.4%
Hypotension:	3.5%

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory Tests

Rarely, mild to moderate transient elevations of enzymes such as alkaline phosphatase, Creatine phosphokinase (CPK), Lactate dehydrogenase (LDH), Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) have been noted after treatment with nifedipine. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Infrequent reversible elevations in Blood Urea Nitrogen (BUN) and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency taking nifedipine.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported with nifedipine rarely (≥0.01% and ≤1%).

Rare instances of allergic hepatitis and cholestasis with or without jaundice have been reported in patients treated with nifedipine.

Gingival hyperplasia similar to that caused by diphenylhydantoin has been reported in patients treated with nifedipine. The lesions usually regressed on discontinuation of the drug. However, on occasion gingivectomy was necessary.

Gynecomastia has been observed rarely in older men on long-term therapy, but has so far always regressed completely on discontinuation of the drug.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. Anaphylaxis has been reported rarely.

In post marketing experience, there have been rare reports of exfoliative dermatitis and Stevens-Johnson Syndrome. Gastrointestinal irritation and gastrointestinal bleeding were also reported; however, the causal relationship is uncertain.

The following adverse events were identified only during post marketing experience with a frequency that could not be estimated: agranulocytosis, epidermal photosensitivity allergic reaction, eye pain, gastro esophageal sphincter insufficiency, hyperglycemia, hypoesthesia, jaundice, leukopenia, toxic epidermal necrolysis, somnolence, toxic palpable purpura, intestinal obstruction, bezoars.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of rifampicin (2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via the CYP 3A4 isoenzyme. Coadministration of nifedipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nifedipine to maintain optimum therapeutic blood levels.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper Name		Source of Evidence	Effect	Clinical Comment
CYP3A4 Substrates	CYP3A4 substrates (e.g., cisapride, tacrolimus, benzodiazepines, imipramine, propafenone, terfenadine, warfarin, flecainide)	N/A	Enzyme substrates of the cytochrome P450 3A4 (CYP3A4), when coadministered with nifedipine, may act like CYP3A4 inhibitors and cause an increase in nifedipine plasma concentrations.	Dose adjustment and monitoring may be required.
	Cisapride	CT	Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.	Upon co-administration of both drugs, blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose considered.

Proper Name		Source of Evidence	Effect	Clinical Comment
	Tacrolimus	C	Tacrolimus has been shown to be metabolized via the cytochrome P450 3A4 system. Data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases.	Upon co-administration of both drugs, tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.
CYP3A4 Inhibitors	CYP3A4 inhibitors: (e.g., azole antifungals (ketoconazole, itraconazole, fluconazole), cimetidine, cyclosporine, erythromycin, fluoxetine, HIV protease inhibitors, nefazodone, quinidine)	N/A	Enzyme inhibitors of CYP3A4 have been shown to cause an increase in nifedipine plasma concentrations, and therefore an increased hypotensive effect of nifedipine.	Dose adjustment and monitoring may be required. Avoid concomitant administration of nifedipine with strong CYP3A4 inhibitors.
	Azole anti-mycotics (e.g., ketoconazole)	T	A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics 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 a decreased first pass metabolism cannot be excluded.

Proper Name		Source of Evidence	Effect	Clinical Comment
CYP3A4 Inhibitors	Cimetidine and Ranitidine	CT	Pharmacokinetic studies have shown that concurrent administration of cimetidine or ranitidine with nifedipine results in significant increases in nifedipine plasma levels (ca. 80% with cimetidine and 70% with ranitidine).	Patients receiving either of these drugs concomitantly with nifedipine should be monitored carefully for the possible exacerbation of effects of nifedipine, such as hypotension. Adjustment of nifedipine dosage may be necessary.
	Diltiazem	CT	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.
	Erythromycin	T	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 drugs.	The potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded
	Clarithromycin	T	A clinical study investigating the potential of a drug interaction between nifedipine and clarithromycin has not yet been performed. In elderly patients (>65 years of age), concomitant use of nifedipine with clarithromycin has been suggested to be associated with an increased incidence of acute kidney injury requiring hospitalization, which may have been caused by increased hypotensive reactions.	Concomitant use should be avoided.

Proper Name		Source of Evidence	Effect	Clinical Comment
	Fluoxetine	T	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
	HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquanavir)	T	A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 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
	Nefazodone	T	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
	Quinidine	CT	The addition of nifedipine to a stable quinidine regimen may reduce the quinidine by 50%, an enhanced response to nifedipine may also occur. The addition of quinidine to a stable nifedipine regimen may result in elevated nifedipine concentrations and a reduced response to quinidine. Some patients have experienced elevated quinidine levels when nifedipine was discontinued.	Patients receiving concomitant therapy of nifedipine and quinidine, or those who had their nifedipine discontinued while still receiving quinidine, should be closely monitored, including determination of plasma levels of quinidine. Consideration should be given to dosage adjustment.

Proper Name		Source of Evidence	Effect	Clinical Comment
	Quinupristin/ Dalfopristin	CT	Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine.	Upon coadministration of both drugs, blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered
	Valproic Acid	T	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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
CYP3A4 Inducers	CYP3A4 Inducers (e.g., Phenytoin, Carbamazepine, Phenobarbital, rifampicin)	N/A	Drugs that are known to induce CYP3A4 may increase the first pass effect or the clearance of nifedipine.	A pharmacodynamic interaction exists, inhibiting effective use of dihydropyridines. Need for careful clinical and laboratory monitoring of patients receiving both classes of medication.

Proper Name		Source of Evidence	Effect	Clinical Comment
	Phenytoin	CT	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.
	Carbamazepine, Phenobarbital	T	No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbital. 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.	Caution and careful monitoring of patients on concomitant therapy is recommended.
	Rifampicin	CT	Rifampicin strongly induces the cytochrome P450 3A4 system. Upon coadministration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened.	The use of nifedipine in combination with rifampicin is therefore contra-indicated

Proper Name		Source of Evidence	Effect	Clinical Comment
Non-CYP3A4 Interactions	Coumarin Anticoagulants	C	There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.	Caution and careful monitoring of patients on concomitant therapy is recommended.
	Beta Adrenergic Blocking Agents	CT	Concomitant administration of nifedipine and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.	Caution and careful monitoring of patients on concomitant therapy is recommended (see 1. INDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular
	Digoxin	CT	Administration of nifedipine with digoxin may lead to reduced digoxin clearance and therefore an increase in the plasma digoxin level.	It is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible “underdosing” or “overdosing” with digitalis.
	Long-acting Nitrates	T	Nifedipine may be safely coadministered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.	No dosage adjustment necessary.

Proper Name		Source of Evidence	Effect	Clinical Comment
	Theophylline	C / CT	Co-administration of nifedipine may cause alterations in theophylline levels.	When both drugs were concomitantly administered, there were no changes in clinical responsiveness of either of these drugs. Monitoring of theophylline serum levels should be considered.

Legend: C = Case Study CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interaction with Grapefruit Juice: Published data indicate that through inhibition of cytochrome P450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers, including nifedipine (see 10.3 Pharmacokinetics, Special Populations and Conditions, Grapefruit juice). Therefore, consumption of grapefruit juice prior to or during treatment with nifedipine should be avoided.

9.6 Drug-Herb Interactions

Hypericum perforatum – Saint John's Wort is an inducer of CYP3A4 and has been shown to cause a decrease in plasma concentrations of nifedipine. Therefore, dosage of nifedipine may have to be increased.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NIFEDIPINE (nifedipine) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). The anti-anginal effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extra-cellular calcium into the cells through specific ion channels. Nifedipine blocks the transmembrane influx of calcium through the slow channels without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Nifedipine does not alter total serum calcium.

The specific mechanism by which nifedipine relieves angina has not been fully determined but it is believed to be brought about largely by its vasodilatory action.

10.2 Pharmacodynamics

Nifedipine dilates the main coronary arteries and coronary arterioles both in normal and ischemic regions and is a potent inhibitor of coronary artery spasm. This property increases myocardial oxygen delivery and is responsible for the effectiveness of nifedipine in vasospastic angina.

Nifedipine, by its vasodilatory action on peripheral arterioles, reduces the total peripheral vascular resistance. This reduces the workload of the heart and thus reduces the myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of nifedipine in chronic stable angina.

The negative inotropic effect of nifedipine is usually not of major clinical significance because the drug's vasodilating properties evoke at therapeutic doses a baroreceptor-mediated reflex tachycardia which tends to counterbalance this negative inotropic effect.

Although nifedipine causes a slight depression of sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

Inhibition of Transmembrane Ca^{++} Influx

Nifedipine has been shown in isolated preparations to restrict the transmembrane calcium ion influx during excitation-contraction coupling in both cardiac and vascular smooth muscles.

10.3 Pharmacokinetics

Absorption

In human, oral administration of 10 mg ^{14}C nifedipine resulted in more than 90% absorption of the drug. Radioactivity was detectable in the serum 20 minutes after oral ingestion and peak serum levels were reached in 1 to 2 hours. 70 to 80% of the activity was eliminated via the kidneys and the remainder via the feces.

The bi-exponential analysis of the disappearance of nifedipine in the plasma yields an initial fast half- life (t½ß) of 2.5 to 3 hours and a terminal slow half-life (t½α) of 5 hours.

Distribution

Protein binding of circulating nifedipine exceeds 90%.

Metabolism

Nifedipine is metabolized by the cytochrome P450 enzyme system, predominantly via CYP 3A4, but also by CYP 1A2 and CYP 2A6 isoenzymes.

Studies in human, dog and rat showed that nifedipine is almost completely metabolized in the body. It is transformed into two pharmacologically inactive metabolites. The main metabolite is the hydroxycarboxylic acid derivative which represents about 95%, the other is the corresponding lactone, which represents about 5%.

Compounds found in grapefruit juice inhibit the cytochrome P450 system, especially isoenzyme CYP 3A4. In a grapefruit juice-nifedipine interaction study in healthy male volunteers, pharmacokinetics of nifedipine showed significant alteration. Following administration of a single dose of nifedipine 10 mg with 250 mL of grapefruit juice, the mean value of nifedipine AUC increased by 34% and the T_{max} increased from 0.8 hours to 1.2 hours, as compared to water (see 9.5 Drug-Food Interactions, Interaction with Grapefruit Juice).

Elimination

The acid form is mainly excreted in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion.

Special Populations and Conditions

- **Hepatic Insufficiency:** Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Pharmacokinetic studies in patients with hepatic cirrhosis showed a clinically significant alteration in the kinetics of nifedipine (prolonged elimination half life and decreased total clearance). The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with hepatic impairment. In these patients, there is a considerable risk of accumulation (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- **Renal Insufficiency**

  The pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in hemodialysis or CAPD (continuous ambulatory peritoneal dialysis) have not reported significantly altered pharmacokinetics of nifedipine.

11 STORAGE, STABILITY AND DISPOSAL

The capsules should be stored between 15°C and 25°C. Avoid freezing. Protect from light.

NIFEDIPINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

Keep out of reach and sight of children.

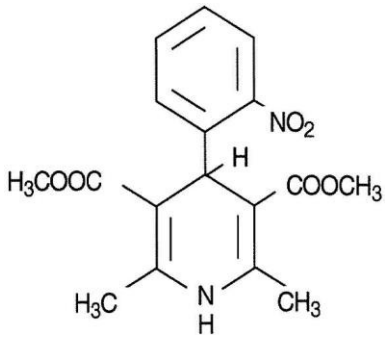
12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Nifedipine
Chemical name:	1,4-dihydro-2,6-dimethy1-4-(2-nitropheny1)-3,5-pyridine-dicarboxylic acid dimethyl ester
Molecular formula and molecular mass:	$C_{17}H_{18}N_2O_6$ and 346.3 g/mol
Structural formula:	
Physicochemical properties:	Nifedipine is a pyridine dicarboxylic acid dimethylester. It is a fine yellowish powder, practically insoluble in water but soluble in ethanol. It is light-sensitive, and when exposed, is converted to a pharmacologically inactive pyridine derivative via an intramolecular redox process.

14 CLINICAL TRIALS

14.2 Study Results

See 14.3 Comparative Bioavailability Studies

14.3 Comparative Bioavailability Studies

A randomized, two treatment, single-dose, crossover comparative bioavailability study of APO-NIFEDIPINE 10 mg Capsule (Apotex Inc.) with ADALAT 10 mg Capsule (Miles Canada Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from the 24 subjects that were included in the statistical analysis are presented in the following table:

Table 3 - Summary Table of the Comparative Bioavailability Data

Nifedipine (2 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test**[1]	**Reference**[2]	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*h/mL)	264.0 282.2 (39.0)	280.6 296.1 (34.9)	94.2	85.7 – 103.7
AUC_I (ng*h/mL)	279.0 296.6 (37.1)	295.4 311.9 (34.5)	94.4	86.3 – 103.4
C_{MAX} (ng/mL)	179.3 192.7 (38.0)	180.9 199.6 (42.1)	99.1	89.5 – 109.9
T_{MAX}[3] (h)	0.58 (0.42 – 1.00)	0.50 (0.42 – 1.50)		
$T_{½}$[4] (h)	3.10 (50.88)	2.96 (43.92)		

[1] Apo-Nifedipine 10 mg Capsule (Apotex Inc.)
[2]Adalat 10 mg Capsule (Miles Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as arithmetic means (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity Studies

Table 4 - Oral LD_{50} Values of Nifedipine

Animal Species	Sex	Dose Level (mg/kg) oral administration	LD_{50} mg/kg
Albino Mice	F	623 – 1604	1000
Albino Mice	M	739 – 1354	1000
Albino Mice	Combined sexes	831 – 1204	1000
Albino Rats	F	3726 – 4962	4300
Albino Rats	M	5294 – 7261	6200
Albinot Rats	Combined sexes	4576 - 5463	5000

[1] Identity of the test product.
[2] Identity of the reference product, including the manufacturer, and origin (country of purchase).

The oral LD_{50} of nifedipine in albino mice was calculated to be 1000 mg/kg regardless of sex; in rats 6200 mg/kg and 4300 mg/kg for males and females respectively.

In mice, most deaths occurred within 24 hours of dosing while in rats, deaths occurred between days 2 and 9 post-dosing. In mice, principal signs of toxicity included ptosis, piloerection, hunching of the back, dyspnea, abdominal distention, tremor and reduced motor activity. In rats, principal signs of toxicity included darkening of the liver, spleen and/or G.I. tract, reddening of the lungs, adrenals, thymus and/or intestines, G.I. tract distention and in some animals, ascites. In both species, animals killed routinely at the end of the studies revealed no abnormalities upon necropsy.

Subacute Toxicity Studies

In rats, oral doses of 0.5 to 100 mg/kg/day nifedipine for 13 weeks did not induce significant adverse effects. Similar results were obtained in dogs treated with 0.5 to 50 mg/kg/day nifedipine for 13 weeks.

Carcinogenicity

Nifedipine was administered orally to dogs at dosages of 2.5, 20 and 100 mg/kg/day for 52 weeks. No indication of toxic damage caused by nifedipine was found.

In a 2–year study, nifedipine was administered orally to male and female rats in the diet at dosages of 5 to 9, 29 to 39, and 156 to 210 mg/kg/day. In the lowest dose group, nifedipine was without toxic effects. The higher dosage led to dose-dependent, significant weight losses. An increased mortality was found in the 156 to 210 mg/kg dose group, especially in the females. The pathological- anatomical examination of the dead animals showed a hypotonia or atonia of the musculature of the small intestine. An increase in the weight of the adrenal glands of male rats was also observed in this dose group. Histopathological examinations revealed no organ damage related to treatment.

At the end of the study, all rats were examined histopathologically with regards to tumorigenesis. Although the animals in the highest dose group showed no uncommon tumor incidences, this group was considered not suitable for comparison with the other treatment groups because of the high mortality rate. No significant difference were found between the controls and the remaining two treatment groups with respect to the frequency, nature and localization of tumors.

Genotoxicity

Mutagenicity Studies

In the Dominant Lethal test, the oral administration of nifedipine to mice at a dose of 100 mg/kg for 5 consecutive days did not affect fertility rate or post-implantation loss.

In the Micronucleus test, 2 doses of 50 mg/kg or 100 mg/kg nifedipine given orally to mice also did not produce any mutagenic effect. Furthermore, the formation of erythrocytes was not impaired as shown by the polychromatic: normochromatic erythrocyte ratio.

In the Ames' Salmonella/microsome test, nifedipine at doses of up to 12500 mcg per plate did not cause any bacterotoxic effects. Also, a dose-dependent and biologically relevant increase in the number of mutants to a level double that of the negative control was not noted.

Reproductive and Developmental Toxicology

Pregnant mice, rats and rabbits were treated orally with 10, 30 and 100 mg/kg nifedipine from day 6 to day 15 of gestation. In the mouse, at doses of 30 and 100 mg/kg there was an increase in the number of fetal resorptions. Fetal malformations in the form of cleft palate and rib deformities occurred at all dose levels in a dose related fashion. (Cleft palate occurred in 5/218 controls, 13/190 at 10 mg/kg, 22/112 at 30 mg/kg and 3/3 at 100 mg/kg).

In the rat, the dose of 30 mg/kg was not toxic to pregnant dams, but caused reduced fetal weight and increased fetal loss. The dose of 100 mg/kg produced malformations in the fetuses from 20% of the mother animals. In a total of 11 fetuses, 10 showed malformation of the front or hind paws (ectrodactyly, oligodactyly and adactyly) and one developed a severe malformation of the sinciput.

In the rabbit, there was a dose-dependent anorexia and weight loss in mothers during the dosing period. At 30 and 100 mg/kg, reduced litter size and weight and increased fetal loss were evident.

Studies on pregnant rhesus monkeys with oral doses of 2 (1 animal) or 6 mg/kg/day (4 animals) revealed no teratogenic effects. The placentas were poorly developed in dosed animals.

Pre- and post-natal studies on rats with daily doses of 3, 10, 30 and 100 mg/kg showed that nifedipine caused significant prolongation of the gestation period at dosage of 10 mg/kg upwards and a decrease in litter size. The post-natal development of the newborn animals was impaired when doses of 30 mg/kg or more had been administered. All offspring in the 100 mg/kg group died.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NIFEDIPINE

nifedipine capsules

Read this carefully before you start taking **NIFEDIPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NIFEDIPINE**.

What is NIFEDIPINE used for?

NIFEDIPINE is used in adults to control chest pain (angina):

- caused by temporary tightening (spasm) of the muscles in the wall of the artery that sends blood to the heart (coronary artery).
- that most often occurs with physical activity or emotional stress (chronic stable angina). It can be used with other chest pain medicines when those medicines do not provide enough benefit on their own. NIFEDIPINE is normally used in patients who have tried beta blockers and/or nitrates for their chest pain, but did not receive benefits, or had bad side effects.

How does NIFEDIPINE work?

NIFEDIPINE belongs to a group of medicines called “calcium channel blockers” or “calcium antagonists”. It works by relaxing and expanding the arteries supplying the heart. This allows more blood and oxygen to reach the heart and decreases the strain on it. Your angina attacks (chest pain) will be less severe and less frequent if there is less strain on the heart.

What are the ingredients in NIFEDIPINE?

Medicinal ingredients: Nifedipine.

Non-medicinal ingredients: Benzyl alcohol, FD&C yellow #6, gelatin, glycerin, iron oxide yellow, lemon oil, mannitol, polyethylene glycol, sorbitan sorbitol solution, titanium dioxide and white ink.

NIFEDIPINE comes in the following dosage forms:

Capsules: 5 mg and 10 mg

Do not use NIFEDIPINE if:

- you are allergic to nifedipine, or to any of the other ingredients in NIFEDIPINE.
- you are allergic to medicines that are similar to NIFEDIPINE (i.e., dihydropyridines calcium antagonists) such as amlodipine, clevidipine, felodipine, isradipine, and nimodipine.
- you are pregnant, think you might be pregnant or plan on becoming pregnant.

- you are a women of childbearing potential and are not using an adequate method of birth control.
- you are breast-feeding or planning to breast-feed.
- you are taking rifampicin (used to treat bacterial infections, including tuberculosis).
- you have recently had a heart attack.
- you are going into cardiovascular shock (your heart suddenly cannot pump enough blood and oxygen to the brain and other vital organs).
- you have very low blood pressure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NIFEDIPINE. Talk about any health conditions or problems you may have, including if you:

- have a history of or are prone to low blood pressure.
- have high blood pressure.
- have had or will have surgery under general anaesthesia.
- have obstructive coronary artery disease (gradual narrowing or closing of arteries that supply the heart with blood due to plaque buildup).
- have unstable angina (sudden chest pain that occurs at rest and gets increasingly worse).
- have recently stopped taking beta blockers (medicines used to treat high blood pressure and other circulatory problems). You may experience withdrawal symptoms, including increased chest pain. Starting treatment with NIFEDIPINE may not prevent these withdrawal symptoms and may even make them worse.
- have a severe heart condition such as heart failure or aortic stenosis (narrowing of a valve in your heart).
- have a history of poor blood circulation in the brain.
- have diabetes.
- have liver problems.
- are a man and are planning or currently trying to father a child by in vitro fertilization.

Other warnings you should know about:

NIFEDIPINE can cause serious side effects, including:

- **Hypotension** (low blood pressure): This can occur after your first dose or after your dose is increased. Your risk may be greater if you also take beta blockers. Tell your healthcare professional if you experience excessive symptoms of low blood pressure, including fainting. They may adjust your dose or stop your treatment with NIFEDIPINE altogether.

- **Angina pectoris** (chest pain) and **Myocardial infarction** (heart attack): In rare cases, NIFEDIPINE can cause chest pain that is new or worse after your first dose or after your dose is increased. Heart attack can also occur. The risk is greater if you have severe

heart disease. If you experience chest pain, stop taking NIFEDIPINE and seek medical help **right away**.

- **Peripheral edema** (swelling of the extremities caused by fluid retention): This mainly occurs in the legs and feet. If you experience swelling in your extremities (including arms and hands), tell your healthcare professional **right away**. They may prescribe you a diuretic (a "water pill") to treat this condition.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

Diabetes: If you have diabetes, NIFEDIPINE may affect your blood sugar control. Closely monitor your blood sugar while taking NIFEDIPINE. Tell your healthcare professional if you notice that you have difficulty controlling your blood sugar levels during your treatment. They may adjust your dose of NIFEDIPINE.

Fertility (male): NIFEDIPINE may affect your chance to father a child. Talk to your healthcare professional if this is important to you.

Birth control (female): NIFEDIPINE may cause harm to an unborn child. If you are a women of childbearing potential, you must use an effective method of birth control while taking NIFEDIPINE. Ask your healthcare professional which birth control method is right for you.

Driving and using machines: NIFEDIPINE can decrease your blood pressure causing light-headedness, dizziness and fainting. These can occur more often after your first dose, when your dose is increased, or in combination with alcohol. Before you drive or do tasks that require special attention, wait until you know how you respond to NIFEDIPINE.

Check-ups and testing: You will have regular visits with your healthcare professional while you are taking NIFEDIPINE to monitor your blood pressure and heart rate. If you have liver problems, they may also do blood tests to monitor the health of your liver during treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take NIFEDIPINE if: • you are taking rifampicin (used to treat bacterial infections, including tuberculosis) as it may reduce the effect of nifedipine.

The following may also interact with NIFEDIPINE:

- medicines used to treat high blood pressure and/or chest pain, including other calcium

channel blockers (e.g., diltiazem) and beta blockers (e.g., atenolol, metoprolol, labetalol, propranolol).
- medicines used to treat fungal infections with a name ending in “azole” (e.g., ketoconazole, itraconazole, fluconazole).
- benzodiazepines, used to treat anxiety, seizures and insomnia.
- medicines used to treat ulcers of the stomach and intestines (e.g., cimetidine, ranitidine).
- medicines used to suppress the immune system (e.g., cyclosporine, tacrolimus).
- digoxin, used to treat various heart conditions.
- medicines used to treat bacterial infections (e.g., clarithromycin, erythromycin, quinupristin/dalfopristin). Taking clarithromycin with NIFEDIPINE may increase your risk of kidney problems if you are elderly.
- medicines used to treat an irregular heartbeat (e.g., flecainide, propafenone, quinidine).
- medicines used to treat depression (e.g., imipramine, fluoxetine, nefazodone).
- medicines used to control seizures (e.g., phenobarbital, phenytoin, valproic acid, carbamazepine).
- medicines used to treat HIV/AIDS (e.g., ritonavir, amprenavir, indinavir, nelfinavir, saquinavir).
- terfenadine, used to treat allergies.
- theophylline, used to treat asthma and other lung problems.
- warfarin, used to prevent blood clots.
- opioid medicines, used to relieve pain (e.g., fentanyl).
- St. John’s Wort, a herbal remedy.
- grapefruit or grapefruit juice. Do not eat grapefruit or drink grapefruit juice during your treatment with NIFEDIPINE.
- alcohol.

How to take NIFEDIPINE:

- Take NIFEDIPINE exactly as directed by your healthcare professional.
- Swallow the capsules whole by mouth.

Usual dose:

The starting dose is one 10 mg capsule, three times daily.

The usual dosage range is 10 mg to 20 mg, three times daily. Your healthcare professional may adjust your dose depending on how you respond to NIFEDIPINE.

The maximum daily dose is 120 mg.

Overdose:

Signs of an overdose with NIFEDIPINE may include:

- low blood pressure that can lead to shock (rapid breathing, pale skin cold and sweaty skin). It can be accompanied with a buildup of fluids in the lungs (difficulty breathing, especially while lying down).

- high blood sugar (increased thirst, dry mouth, needing to pee frequently).
- buildup of acid in the body (confusion, rapid heartbeat, feeling sick, headache, long and deep breaths).
- low levels of oxygen in your body tissues (shortness of breath, headache, confusion or restlessness).
- slow or rapid heartbeat.
- decreased consciousness or coma.

If you think you, or a person you are caring for, have taken too much NIFEDIPINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten or missed a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your next dose at the usual time. Do NOT double the dose to make up for a missed dose.

What are possible side effects from using NIFEDIPINE?

These are not all the possible side effects you may have when taking NIFEDIPINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with NIFEDIPINE include:

- blurry vision
- eye pain
- breast enlargement in men
- feeling dizzy, lightheaded, weak or nervous
- stuffy nose, fever, sweating and chills
- flushing (reddening of the skin) or feeling unusually warm
- headache
- joint stiffness, muscle pain and cramps
- reduced sensation in a body part
- rash, itchy skin, hives, skin irritation, sensitivity to the sun
- shaking
- sleep problems
- enlargement of the gums

NIFEDIPINE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Dyspnea (shortness of breath)		✓	
Abdominal pain		✓	
Nausea or vomiting		✓	
Heartburn		✓	
Hypotension (low blood pressure): dizziness, fainting, lightheadedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)			✓
Peripheral edema (swelling of the extremities caused by fluid retention): swollen or puffy hands, ankles, feet or legs, feeling heavy, achy or stiff	✓		
UNCOMMON			
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide.		✓	
Diarrhea		✓	
Constipation		✓	
Syncope (fainting)			✓
RARE			
Angina pectoris attack (not enough oxygen to the heart muscle): pain or pressure in the chest, discomfort in the shoulder, arms, back, throat, jaw or teeth			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Gastrointestinal bleeding and irritation: blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			✓
Liver disorder (including hepatitis and cholestasis): yellowing of the skin or eyes (jaundice), dark urine, pale stools, abdominal pain, nausea, vomiting, loss of appetite		✓	
VERY RARE			
Allergic reaction/Angioedema: difficulty breathing or swallowing, rash or hives (redness, intense itching and burning), swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs			✓
UNKNOWN FREQUENCY			
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		✓	
Irregular or fast heartbeat			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
fatigue, lightheadedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			
Pulmonary edema (excess fluid in the lungs): difficulty breathing that worsens with activity or when lying down, extreme shortness of breath, wheezing or gasping for breath, cold clammy skin, irregular heartbeat, cough that produces frothy sputum, blue-tinged lips			✓
Toxic Epidermal Necrolysis (TEN) (severe skin reaction): redness, blistering and/or peeling of large areas of the skin, especially in the mouth and eyes			✓
Intestinal obstruction (blockage that stops or impairs passage of contents of intestines): cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C and 25°C. Avoid freezing. Protect from light.

Keep out of reach and sight of children.

If you want more information about NIFEDIPINE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc. 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

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