PRODUCT MONOGRAPH

[Pr] MYLAN-NIFEDIPINE EXTENDED RELEASE

Nifedipine Extended Release Tablets

20 mg, 30 mg and 60 mg

USP

Antianginal/Antihypertensive Agent

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

Date of Revision: December 22, 2017

Submission Control No.: 195515

Table of Contents

[Pr] MYLAN-NIFEDIPINE EXTENDED RELEASE

Nifedipine Extended Release Tablets

20 mg, 30 mg and 60 mg

USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	extended release tablets / 20 mg, 30 mg and 60 mg	**20 mg:** cellulose acetate, colloidal silicon dioxide, FD&C Blue #1, hydroxypropylcellulose, hydroxypropyl methylcellulose, iron oxide black, iron oxide red, magnesium stearate, polydextrose, polyethylene glycol, polyethylene oxide, propylene glycol, sodium chloride, sodium stearyl fumarate and titanium dioxide. **30 mg and 60 mg:** cellulose acetate, colloidal silicon dioxide, glycerol triacetate, hydroxypropylmethylcellulose, iron oxide black, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate, povidone, propylene glycol, sodium chloride and titanium dioxide.

INDICATIONS AND CLINICAL USE

MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) is indicated for:

Chronic Stable Angina

MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) is indicated in the 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 nitrates, or who cannot tolerate these agents.

MYLAN-NIFEDIPINE EXTENDED RELEASE may be used in combination with beta blocking drugs in patients with chronic stable angina. However, 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 **WARNINGS AND PRECAUTIONS**).

Hypertension

MYLAN-NIFEDIPINE EXTENDED RELEASE is indicated in the management of mild to moderate essential hypertension. MYLAN-NIFEDIPINE EXTENDED RELEASE should normally be used in those patients in whom treatment with diuretics or beta blocker has been ineffective, or has been associated with unacceptable adverse effects.

MYLAN-NIFEDIPINE EXTENDED RELEASE can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of nifedipine extended release tablets with a diuretic has been found compatible and has shown added antihypertensive effect. Concurrent administration of low doses of nifedipine extended release tablets and enalapril has been shown to produce an enhanced antihypertensive effect with no additional safety concerns when compared to that observed with either of the monotherapies.

Safety of concurrent use of nifedipine extended release tablets with other antihypertensive agents has not been established.

CONTRAINDICATIONS

MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) is contraindicated in:

- Pregnancy, during lactation, and in women of childbearing potential. 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 **TOXICOLOGY, Reproductive Toxicology**).

- Patients who are hypersensitive to nifedipine, or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

- Patients with a known hypersensitivity to other dihydropyridines calcium antagonists, because of the theoretical risk of cross-reactivity.

- Patients with severe hypotension or cardiovascular shock.

- Combination with rifampicin because insufficient plasma levels of nifedipine may result due to enzyme induction.

- Patients with a Kock pouch (ileostomy after proctocolectomy).

- MYLAN-NIFEDIPINE EXTENDED RELEASE should not be administered to patients with moderate or severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

- MYLAN-NIFEDIPINE EXTENDED RELEASE should not be administered to patients with severe gastrointestinal (GI) obstructive disorders (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Cardiovascular

The safety of nifedipine prolonged release tablets has not been established in patients with malignant hypertension.

Excessive Hypotension in Patients with Angina

Since MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) lowers peripheral vascular resistance and blood pressure, MYLAN-NIFEDIPINE EXTENDED RELEASE should be used cautiously in patients with angina who are prone to develop hypotension and those with a history of cerebrovascular insufficiency. Occasionally patients have had excessive and poorly tolerated hypotension. Syncope has been reported (see **ADVERSE REACTIONS**). 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 **CONTRAINDICATIONS**).

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine, with a beta blocker, 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.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina.

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 the response is not established.

Since there has not been a study of nifedipine extended release tablets in acute myocardial infarction reported, similar effects of MYLAN-NIFEDIPINE EXTENDED RELEASE to that of immediate-release nifedipine cannot be excluded. Immediate-release nifedipine is contraindicated in acute myocardial infarction.

Beta-Blocker Withdrawal

Patients with angina recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of treatment with MYLAN-NIFEDIPINE EXTENDED RELEASE 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 initiation of nifedipine. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning MYLAN-NIFEDIPINE EXTENDED RELEASE.

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, MYLAN-NIFEDIPINE EXTENDED RELEASE should be used cautiously in patients with severe heart failure. Rarely have patients receiving a beta-blocker 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 MYLAN-NIFEDIPINE EXTENDED RELEASE in patients with these conditions.

Hypotension/Heart Rate

Because MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) 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.

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 extended release tablets (see **ADVERSE REACTIONS**). This edema occurs primarily in the lower extremities and may respond to diuretic therapy. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Gastrointestinal

Patients with Pre-Existing Gastrointestinal Narrowing

Since the MYLAN-NIFEDIPINE EXTENDED RELEASE delivery system contains a non-deformable material, caution should be used when administering MYLAN-NIFEDIPINE EXTENDED RELEASE in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of nifedipine extended release tablets. In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders. Bezoars can occur in very rare cases and may require surgical intervention. MYLAN-NIFEDIPINE EXTENDED RELEASE should be used with caution in patients with inflammatory bowel disease, Crohn's disease, or with a history of gastrointestinal obstruction, esophageal obstruction, or with decreased diameter of the gastrointestinal lumen.

When doing barium contrast X-ray, MYLAN-NIFEDIPINE EXTENDED RELEASE may cause false positive effects (e.g., filling defects interpreted as polyp).

Sexual Function/Reproduction

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.

Special Populations

Pregnant Women

The use of MYLAN-NIFEDIPINE EXTENDED RELEASE is contraindicated during pregnancy (see **CONTRAINDICATIONS**).

There are no adequate and well-controlled studies of nifedipine extended release tablets in pregnant women. 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 **CONTRAINDICATIONS**).

Nursing Women

The use of nifedipine is contraindicated during lactation (see **CONTRAINDICATIONS**).

Pediatrics (< 18 years of age)

The safety and efficacy of nifedipine extended release tablets in children below 18 years of age has not been established.

Geriatrics

MYLAN-NIFEDIPINE EXTENDED RELEASE should be administered cautiously to elderly patients, especially to those with a history of hypotension or cerebral vascular insufficiency.

Diabetic Patients

The use of MYLAN-NIFEDIPINE EXTENDED RELEASE in diabetic patients may require adjustment for their control.

Hepatic Insufficiency

MYLAN-NIFEDIPINE EXTENDED RELEASE should be used with caution in patients with mild impaired liver function, and a dose reduction may be required (see **ACTION AND CLINICAL PHARMACOLOGY**, ***Special Populations***, ***Hepatic Insufficiency***). Close monitoring of response and metabolic effect should apply.

The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment. As there is no nifedipine formulation (< 20 mg/dose) to up-titrate patients with moderate or severe hepatic impairment, MYLAN-NIFEDIPINE EXTENDED RELEASE should be contraindicated in patients with moderate or severe hepatic impairment (see **CONTRAINDICATIONS**, **DOSAGE AND ADMINISTRATION, Recommended Dose and**

Dosage Adjustment, and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Insufficiency**).

Concomitant Use with Strong Inhibitors of CYP 3A4

Use of MYLAN-NIFEDIPINE EXTENDED RELEASE 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 **DRUG INTERACTIONS**). 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).

Monitoring and Laboratory Tests

Hypotension/Heart Rate

Because MYLAN-NIFEDIPINE EXTENDED RELEASE 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 **WARNINGS AND PRECAUTIONS, Cardiovascular**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety information from clinical trials as well as from post-marketing surveillance and other sources is analyzed and reflected in the following section. Frequencies of occurrence are calculated from clinical trial analysis.

The most common adverse drug reactions (ADRs) are headache, edema, vasodilation, and constipation. None of these ADRs are considered severe.

The most severe reported ADRs are “agranulocytosis”, “leukopenia” and “toxic epidermal necrolysis”. These ADRs were reported from post-marketing surveillance and require immediate medical intervention.

“Angina pectoris” (chest pain) (frequency: common) and “intestinal obstruction” (frequency: unknown) require immediate medical intervention.

The ADRs "hypotension", "syncope" (frequency: uncommon (≥ 1/1,000 to < 1/100)) and "angioedema" (frequency: unknown) require immediate medical intervention.

"Allergic reaction" (frequency: uncommon) is associated with nifedipine and might require immediate medical intervention.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Angina

In 257 chronic stable angina patients treated in controlled and long-term open studies with nifedipine extended release tablets, adverse effects were reported in 30.0% of patients and required discontinuation of therapy in 8.5% of patients.

The most common adverse effects were: edema (10.1%), headache (3.1%), angina pectoris (3.1%).

The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis:

Cardiovascular: Palpitation (2.3%), tachycardia, myocardial infarction, ventricular arrhythmia, extrasystoles, dyspnea, chest pain.

In patients with angina, rarely, 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.

Central Nervous System: Dizziness (2.3%), hypoesthesia (1.2%), confusion, insomnia, somnolence, nervousness, asthenia, hyperkinesia.

Gastrointestinal: Constipation (1.9%), dyspepsia (1.2%), abdominal pain (1.2%), diarrhea, nausea, melena.

Genito-urinary: Impotence, hematuria, polyuria, dysuria.

Musculo-skeletal: Leg cramps, paresthesia, myalgia, arthralgia.

Dermatologic: Rash, pruritus.

Other: Fatigue (1.2%), pain, periorbital edema.

Hypertension

In 661 hypertensive patients treated in controlled trials with nifedipine extended release tablets, adverse effects were reported in 54.0% of patients and required discontinuation of therapy in 11.9% of patients. The majority of adverse effects reported occurred within the first three months of therapy.

The most common adverse effects reported with nifedipine extended release tablets were edema, which was dose related and ranged in frequency from approximately 10 to 30% in the 30 to 120 mg dose range, headache (16.6%), fatigue (6.2%), dizziness (4.4%), constipation (3.5%), and nausea (3.5%).

The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis:

Cardiovascular: Flushing (2.4%), palpitation (2.3%), tachycardia (1.2%), chest pain (1.1%), ventricular arrhythmia, hypotension, syncope.

Central Nervous System: Insomnia (1.8%), nervousness (1.8%), somnolence (1.5%), depression, tremor, decreased libido, migraine, vertigo, amnesia, anxiety, impaired concentration, twitching, ataxia, hypertonia, paresthesia, hypoesthesia.

Gastrointestinal: Dyspepsia (1.5%), flatulence (1.5%), abdominal pain (1.4%), dry mouth (1.1%), diarrhea, vomiting, thirst, melena, eructation, weight increase.

Genito-urinary: Impotence (1.5%), polyuria (1.5%), dysuria, nocturia, oliguria, urinary incontinence, urinary frequency, menstrual disorder.

Musculo-skeletal: Arthralgia, back pain, myalgia.

Special Senses: Abnormal vision, abnormal lacrimation, taste disturbance, conjuctivitis, tinnitus.

Dermatologic: Rash (2.3%), pruritus (1.1%), erythematous rash, alopecia.

Respiratory: Dyspnea (1.7%), bronchospasm, pharyngitis, upper respiratory tract infection, epistaxis.

Other: Leg cramps (2.7%), pain (2.7%), asthenia (2.0%), face edema, gout, allergy, fever, breast pain.

Abnormal Hematologic and Clinical Chemistry Findings

Rare, usually transient, but occasionally significant elevations of enzymes such as CPK, AST, and ALT have been noted. The relationship to drug therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported.

An increase (5.4%) in mean alkaline phosphatase was noted in patients treated with nifedipine extended release tablets. This was an isolated finding not associated with clinical symptoms and rarely resulted in values which exceeded the upper limit of the normal range.

Serum potassium was unchanged in patients receiving nifedipine extended release tablets in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine decreases platelet aggregation in vitro. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine-treated patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs tests, with or without associated hemolytic anemia, have been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to therapy with nifedipine extended release tablets is uncertain in most cases, but probable in some.

Post-Market Adverse Drug Reactions

The following adverse events have been reported with nifedipine rarely.

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 postmarketing 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 postmarketing experience with a frequency that could not be estimated: agranulocytosis, epidermal photosensitivity allergic reaction, eye pain, gastro esophageal sphincter insufficiency, hyperglycemia, hypoaesthesia, jaundice, leukopenia, toxic epidermal necrolysis, somnolence, toxic palpable purpura, intestinal obstruction, bezoars.

An open, non-randomized postmarketing surveillance study (EXACT), involving 1700 mild to moderate hypertensive patients, was conducted in the offices of general practitioners across Canada. Patients were enrolled in the study if they had been previously treated with either single or dual antihypertensive therapy and the physician considered nifedipine extended release tablets an appropriate monotherapy. Patients were to be started on nifedipine extended release tablets 30 mg. If after 3 or 6 weeks of therapy with nifedipine extended release tablets 30 mg, blood pressure was uncontrolled (ie, sitting diastolic blood pressure was > 95 mmHg), then the patient was given 60 mg nifedipine extended release tablets at the physician's discretion.

Twelve patients were started immediately on nifedipine extended release tablets 60 mg. Patients were followed for 20 weeks. Adverse events were reported in 605/1700 patients (35.6%). These adverse events were typical of those seen with the dihydropyridine class of calcium channel blockers (edema, headache, dizziness) and are related to the vasodilatory properties of this class of compounds.

The following is a summary of adverse effects which occurred with a frequency of ≥1% during this 20-week study.

Table 2 – Summary of adverse effects which occurred with a frequency of ≥1% during postmarketing surveillance study (EXACT)

Adverse Effect	All Patients (n = 1700)	
	%	(n)
Patients with ≥ 1 Adverse Effect	35.6	(605)
Headache	12.2	(207)
Peripheral Edema	8.1	(137)
Dizziness	2.9	(50)
Asthenia	2.8	(48)
Vasodilation	2.5	(43)
Constipation	2.4	(40)
Palpitations	1.7	(29)
Nausea	1.5	(26)
Anxiety	1.2	(20)
Dyspepsia	1.1	(18)
Insomnia	1.1	(18)
Tachycardia	1.0	(17)

The following table illustrates the time period during which the adverse effects in the preceding table occurred. The majority of the adverse effects occurred during the first 3 weeks that the patients received nifedipine extended release tablets. The incidence rate of adverse effects continued to diminish as the length of exposure to nifedipine extended release tablets increased.

Adverse Effects Occurring During Each Time Period

Table 3 - Summary of adverse effects with a frequency of ≥1% during each time period in the postmarketing surveillance study (EXACT)

Adverse Events	Unknown		0 - 3 Weeks		3 - 6 Weeks		6 - 12 Weeks		12 - 20 Weeks	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache	7	(0.7)	148	(13.8)	41	(3.8)	22	(2.1)	6	(0.6)
Peripheral Edema	2	(0.2)	56	(5.2)	42	(3.9)	33	(3.1)	18	(1.7)
Dizziness	2	(0.2)	27	(2.5)	11	(1.0)	7	(0.7)	4	(0.4)
Asthenia	2	(0.2)	23	(2.1)	15	(1.4)	9	(0.8)	0	(0)
Vasodilatation	2	(0.2)	27	(2.5)	5	(0.5)	4	(0.4)	6	(0.6)
Constipation	0	(0)	25	(2.3)	8	(0.7)	5	(0.5)	3	(0.3)
Palpitations	1	(0.1)	17	(1.6)	6	(0.6)	2	(0.2)	4	(0.4)
Nausea	0	(0)	21	(2.0)	4	(0.4)	2	(0.2)	0	(0)
Anxiety	2	(0.2)	5	(0.5)	6	(0.6)	2	(0.2)	6	(0.6)
Dyspepsia	1	(0.1)	5	(0.5)	5	(0.5)	5	(0.5)	2	(0.2)
Insomnia	1	(0.1)	6	(0.6)	3	(0.3)	3	(0.3)	6	(0.6)
Tachycardia	1	(0.1)	5	(0.5)	3	(0.3)	6	(0.6)	3	(0.3)

DRUG INTERACTIONS

Drug-Drug Interactions

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydrophyridine calcium channel blockers, undergo biotransformation by the cytochrome P450 system, mainly via the CYP3A4 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. If necessary, an adjustment in the dose of nifedipine may be considered.

Cytochrome P-450 Enzyme Substrates

Drugs known to be biotransformed via cytochrome P450 include: benzodiazepines, cisapride, tacrolimus, imipramine propafenone, terfenadine and warfarin (see Table 4).

Cytochrome P-450 Enzyme Inhibitors

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals (ketoconazole, itraconazole, fluconazole), cimetidine, clarithromycin, cyclosporine, erythromycin, fluoxetine, HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquanavir), nefazodone, and quinidine. Enzyme inhibitors of the cytochrome P450 3A4 system

have been shown to cause an increase in nifedipine plasma concentrations (see Table 4).

Cytochrome P-450 Enzyme Inducers

Enzyme inducers of the cytochrome P450 3A4 system have been shown to cause a decrease in plasma concentrations of nifedipine, e.g. Hypericum perforatum (Saint John's Wort) (see **Drug-Herb Interactions**), phenobarbital, phenytoin, and rifampicin (see Table 4).

Table 4 - Established or Potential Drug-Drug Interactions

Proper Name		Ref	Effect	Clinical Comment
CYP3A4 Substrates	CYP3A4 substrates (e.g., cisapride, tacrolimus, benzodiazepines, imipramine, propafenone, terfenadine, warfarin)	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.
	Tacrolimus	C	Tacrolimus has been shown to be metabolised 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),	N/A	Enzyme inhibitors of CYP3A4 have been shown to cause an increase in nifedipine plasma concentrations, and therefore	Dose adjustment and monitoring may be required. Avoid concomitant

Proper Name		Ref	Effect	Clinical Comment
	cimetidine, cyclosporine, erythromycin, fluoxetine, HIV protease inhibitors, nefazodone, quinidine)		an increased hypotensive effect of nifedipine.	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.
	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.

Proper Name		Ref	Effect	Clinical Comment
	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.
	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	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	When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a

Proper Name		Ref	Effect	Clinical Comment
			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.	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 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.
	Quinupristin/ Dalfopristin	CT	Simultaneous administration of quinupristin/dalfopristin 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

Proper Name		Ref	Effect	Clinical Comment
				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.
	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-

Proper Name		Ref	Effect	Clinical Comment
				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 co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened.	The use of nifedipine in combination with rifampicin is therefore contra-indicated
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	Caution and careful monitoring of patients on

Proper Name		Ref	Effect	Clinical Comment
			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.	concomitant therapy is recommended (see **INDICATIONS AND CLINICAL USE** and **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 co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.	No dosage adjustment necessary.
	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; N/A = Not Applicable

Drug-Food Interactions

Interaction with Grapefruit Juice

The inhibitory effect of grapefruit juice on CYP3A has been described in numerous publications and the corresponding effect on the pharmacokinetics of nifedipine is highly variable. Considering that the increase of AUC and C_{max} of nifedipine may be as large as two-fold, the administration of nifedipine with grapefruit juice should be avoided (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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.

Drug-Lifestyle Interactions

Ability to Drive and Use 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

See **WARNINGS AND PRECAUTIONS, Special Populations** and **DRUG INTERACTIONS, Drug-Drug Interactions**.

Recommended Dose and Dosage Adjustment

In patients with mild impaired liver function, careful monitoring should be performed and a dose reduction may be necessary. As there is no nifedipine formulation (< 20 mg/dose) to up-titrate patients with moderate or severe hepatic impairment, MYLAN-NIFEDIPINE EXTENDED RELEASE is contraindicated in patients with moderate or severe haptic impairment (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Insufficiency**, and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Insufficiency**).

Administration

Dosage should be individualized depending on patient tolerance and response.

MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) must be swallowed whole and should not be bitten or divided.

In general, titration steps should proceed over a 7-14 day period so that the physician can assess the response to each dose level before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided that the patient is closely monitored.

Chronic Stable Angina

Therapy with MYLAN-NIFEDIPINE EXTENDED RELEASE should normally be initiated with 30 mg once daily. Experience with doses greater than 90 mg daily in patients with angina is limited, therefore, doses greater than 90 mg daily are not recommended.

Angina patients controlled on nifedipine capsules alone or in combination with beta blockers may be safely switched to MYLAN-NIFEDIPINE EXTENDED RELEASE tablets at the nearest equivalent daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.

Hypertension

Therapy should normally be initiated with 20 or 30 mg once daily. The usual maintenance dose is 30 to 60 mg once daily. Doses greater than 90 mg daily are not recommended.

Patients switched from nifedipine prolonged action tablets to MYLAN-NIFEDIPINE EXTENDED RELEASE therapy should receive an initial dosage of MYLAN-NIFEDIPINE EXTENDED RELEASE no higher than 30 mg once daily, based on previously prescribed dosing regimen. If clinically warranted, the dosage of MYLAN-NIFEDIPINE EXTENDED RELEASE should be increased to 60 mg once daily. Blood pressure and patient symptoms should be monitored closely following the switch from nifedipine prolonged action tablets to MYLAN-NIFEDIPINE EXTENDED RELEASE.

No "rebound effect" has been observed upon discontinuation of nifedipine extended release tablets. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually under close physician supervision.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

There are several well-documented cases of nifedipine extended-release tablets 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, and cardiogenic shock with pulmonary oedema.

As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority. After oral ingestion, thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Particularly in cases of intoxication with slow-release products like MYLAN-NIFEDIPINE EXTENDED RELEASE, elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MYLAN-NIFEDIPINE EXTENDED RELEASE (nifedipine extended release tablets) is a calcium ion influx inhibitor (calcium channel blocker or calcium ion antagonist).

MYLAN-NIFEDIPINE EXTENDED RELEASE, while similar in appearance to a conventional tablet, nonetheless consists of a semipermeable membrane surrounding an osmotically active drug core with a laser drilled hole extending through the membrane to the tablet core. As water from the gastrointestinal tract enters the tablet through the semipermeable membrane, pressure

increases in the osmotically active core created by the action of swellable polymers upon contact with aqueous solution, forcing release of a drug slurry through the orifice.

Drug delivery is essentially constant as long as the osmotic gradient remains constant and then gradually falls to zero as drug is exhausted from the tablet. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

The antianginal and antihypertensive actions of nifedipine are believed to be related to a 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 extracellular calcium into the cells through specific ion channels. Nifedipine selectively inhibits the transmembrane influx of calcium through the slow channel 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 the muscle cells and an inhibition of the contractile processes. Nifedipine does not alter total serum calcium.

The specific mechanisms by which nifedipine relieves angina and reduces blood pressure have not been fully determined but are believed to be brought about largely by its vasodilatory action.

Pharmacodynamics

Nifedipine dilates the main coronary arteries and coronary arterioles both in normal and ischemic regions resulting in an increase in blood flow and hence in myocardial oxygen delivery.

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

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and subsequent reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.

The negative inotropic effect of nifedipine is usually not of major clinical significance because at therapeutic doses, nifedipine's vasodilatory property evokes a baroreceptor mediated reflex tachycardia which tends to counterbalance this negative inotropic effect. Continued administration of nifedipine to hypertensive patients has shown no significant increase in heart rate.

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 in man. In formal electrophysiologic studies, predominantly in patients with

normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction or sinus node recovery time, or to slow sinus rate.

Pharmacokinetics

Absorption

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate exhibiting zero-order absorption kinetics after nifedipine extended release tablets administration and reach a plateau at approximately six hours after the first dose. For subsequent doses, relatively constant plasma concentrations at this plateau are maintained with minimal fluctuations over the 24-hour dosing interval. About a four-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate-release nifedipine capsule at t.i.d. dosing than with once-daily nifedipine extended release tablets. At steady state the bioavailability of the nifedipine extended release tablet is 86% relative to nifedipine capsules. Administration of the nifedipine extended release tablet in the presence of food slightly alters the early rate of drug absorption but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (ie, short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentrations.

Pharmacokinetics of nifedipine extended release tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food. The bioavailability of the 20 mg tablet is directly proportional to the 30 mg tablet.

Metabolism

Nifedipine is metabolized by the cytochrome P450 enzyme system, predominantly via CYP3A4, but also by CYP1A2 and CYP2A6 isoenzymes.

Compounds found in grapefruit juice inhibit the cytochrome P450 system, especially CYP3A4. 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 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 **DRUG INTERACTIONS: Drug-Food Interactions**).

Excretion

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. The main metabolite (95%) is the hydroxycarbolic acid derivative; the remaining 5% is the corresponding lactone. Only traces (less than 0.1% of the dose) of unchanged nifedipine can be detected in the urine.

Special Populations

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 prolongation of elimination half-life and a decrease in total clearance of nifedipine. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with hepatic impairment (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS: Special Populations: Hepatic Insufficiency**).

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 has not been investigated in patients with severe hepatic impairment (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Insufficiency**).

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.

STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light, humidity and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

MYLAN-NIFEDIPINE EXTENDED RELEASE 20 mg tablets are supplied in cartons containing 3 blister strips of 10 tablets and in HDPE bottles of 30's and 100's.

MYLAN-NIFEDIPINE EXTENDED RELEASE 30 mg tablets are supplied in cartons containing 2 blister strips of 15 tablets and in HDPE bottles of 100's.

MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg tablets are supplied in cartons containing 2 blister strips of 15 tablets and in HDPE bottles of 100's.

Composition

MYLAN-NIFEDIPINE EXTENDED RELEASE 20 mg Tablets
MYLAN-NIFEDIPINE EXTENDED RELEASE 20 mg tablets are pink film-coated, round, biconvex tablets with **M** over **NF2** imprinted in black ink on one side of the tablet and a laser drill hole on either side.

Each tablet contains 20 mg of nifedipine and the following non-medicinal ingredients: cellulose acetate, colloidal silicon dioxide, FD&C Blue #1, hydroxypropylcellulose, hydroxypropyl methylcellulose, iron oxide black, iron oxide red, magnesium stearate, polydextrose, polyethylene glycol, polyethylene oxide, propylene glycol, sodium chloride, sodium stearyl fumarate and titanium dioxide.

MYLAN-NIFEDIPINE EXTENDED RELEASE 30 mg Tablets
MYLAN-NIFEDIPINE EXTENDED RELEASE 30 mg tablets are round, biconvex, pink coated tablets imprinted in black with "KU 260" on one side and laser drill hole on either side.

Each tablet contains 30 mg of nifedipine and the following non-medicinal ingredients: cellulose acetate, colloidal silicon dioxide, glycerol triacetate, hydroxypropylmethylcellulose, iron oxide black, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate, povidone, propylene glycol, sodium chloride and titanium dioxide.

MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg Tablets
MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg tablets are round, biconvex, pink coated tablets imprinted in black with a "KU 261" on one side and laser drill hole on either side.

Each tablet contains 60 mg of nifedipine and the following non-medicinal ingredients: cellulose acetate, colloidal silicon dioxide, glycerol triacetate, hydroxypropylmethylcellulose, iron oxide black, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate, povidone, propylene glycol, sodium chloride and titanium dioxide.

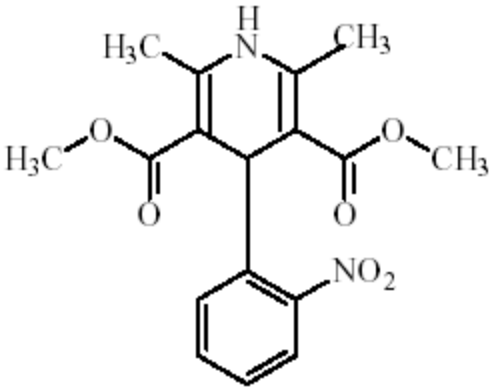
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Nifedipine
Chemical name:	Dimethyl 1,4-dihydro-2,6-dimethyl-4-(o nitrophenyl)- 3,5-pyridinedicarboxylate
Molecular formula and molecular mass:	$C_{17}H_{18}N_2O_6$ 346.33 g/mol

Structural formula:



Physicochemical properties:	Nifedipine is a yellow crystalline powder; it is light-sensitive and practically insoluble in water.

CLINICAL TRIALS

Comparative Bioequivalence Studies

A total of six comparative bioequivalence studies were conducted on MYLAN-NIFEDIPINE EXTENDED RELEASE (Nifedipine Extended Release Tablets) against Adalat® XL® as follows:

- A blinded, randomized, single oral dose, two-treatment, two-period, crossover bioequivalence study of Mylan-Nifedipine Extended Release 20 mg (Mylan Pharmaceuticals ULC) and Adalat® XL® (nifedipine) 20 mg (Bayer Inc.) was performed in healthy, adult Asian male subjects (n=49) under fasting conditions.
- A blinded, randomized, single oral dose, two-treatment, two-period, crossover bioequivalence study of Mylan-Nifedipine Extended Release 20 mg (Mylan Pharmaceuticals ULC) and Adalat® XL® (nifedipine) 20 mg (Bayer Inc.) was performed in healthy, adult Asian male subjects (n=49) under fed conditions.
- A blinded, randomized, single-dose, two way crossover oral bioequivalence study of MYLAN-NIFEDIPINE Extended Release 60 mg tablets and Adalat® XL® (nifedipine) 60 mg tablets was conducted in forty-two (42/50) normal, healthy male and female subjects (age range = 18 – 55) under fed conditions.
- A blinded, randomized, single-dose, two way crossover oral bioequivalence study of MYLAN-NIFEDIPINE Extended Release 60 mg tablets and Adalat® XL® (nifedipine) 60 mg tablets was conducted in forty-six (46/50) normal, healthy male and female subjects (age range = 18 – 55) under fasting conditions.
- A blinded, randomized, multiple-dose, two way crossover oral bioequivalence study of MYLAN-NIFEDIPINE Extended Release 60 mg tablets and Adalat® XL® (nifedipine) 60 mg tablets was conducted in thirty-three (33/38) normal, healthy male and female subjects (age range = 18 – 55) under fasted conditions.
- A blinded, randomized, two treatment, two period, two sequence, single-dose, crossover oral bioequivalence study of Mylan-Nifedipine 30 mg Extended-release tablets and Adalat® XL (nifedipine) 30 mg tablets was conducted in thirty-three (33/40) normal, healthy male and female subjects (age range = 18 – 55) under fasting conditions.

A summary of the results is presented in the following tables.

20 mg bioequivalence study under fasting conditions (male subjects):

Nifedipine (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	405.3 482.9 (64.6)	429.6 512.7 (65.2)	94.4	86.3-103.2
AUC_I (ng·hr/mL)	427.0 499.1 (63.0)	458.1^ 541.7^ (63.9)	93.2^	85.2-102.0^
C_{MAX} (ng/mL)	20.7 23.4 (56.6)	21.9 24.5 (60.9)	94.6	88.9-100.7
T_{MAX}§ (h)	14.4 (57.1)	17.1 (51.2)		
$T_{½}$€ (h)	6.3 (38.1)	6.8^ (32.4)		

* Mylan-Nifedipine Extended Release 20 mg (Mylan Pharmaceuticals ULC).
† Adalat® XL® (nifedipine) 20 mg (Bayer Inc.) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.
€ Expressed as the arithmetic mean (CV%) only.
^ N=47

20 mg bioequivalence study under fed conditions (male subjects):

Nifedipine
(1 x 20 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	431.0 528.2 (68.0)	414.2 500.1 (64.5)	104.1	93.3-116.1
AUC_I (ng·hr/mL)	471.6^ 560.7^ (64.1)	440.2‡ 516.2‡ (63.6)	107.1$	96.4-119.0$
C_{MAX} (ng/mL)	25.6 28.5 (53.5)	24.8 27.5 (48.6)	103.0	95.9-110.6
T_{MAX}§ (h)	11.3 (51.9)	11.8 (58.5)		
$T_{½}$€ (h)	7.0^ (84.7)	6.4‡(34.8)		

* Mylan-Nifedipine Extended Release 20 mg (Mylan Pharmaceuticals ULC).
† Adalat® XL® (nifedipine) 20 mg (Bayer Inc.) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.
€ Expressed as the arithmetic mean (CV%) only.
^ N=47
‡ N=48
$ N=46

Summary of the comparative bioavailability data (60 mg single dose fed study):

Nifedipine 1 x 60 mg Extended-Release Tablets From measured data Uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEST Mylan-Nifedipine Extended Release* 60 mg Tablets	REFERENCE Adalat® XL® † 60 mg Tablets	% Ratio of Geometric Means**	90% Confidence Interval**
AUC_{0-t} (ng·h/mL)	865.3193 992.9385 (53.35)	942.9159 1078.0246 (52.29)	91.8	84.61 – 99.54
AUC_{0-inf} (ng·h/mL)	882.5489 1029.3488 (53.04)	969.5322 1147.35 (49.76)	91.0	83.13 – 99.67
C_{max} (ng/mL)	55.2896 63.4690 (47.75)	48.7187 56.5352 (51.61)	113.5	106.54 – 120.88
T_{max}§ (h)	10.29 (26.68)	10.78 (35.55)		
$T_{½}$§ (h)	9.23 (35.65)	8.00 (26.32)		

* MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg Tablets (Manufactured by Schwarz, USA for Mylan Pharmaceuticals ULC, Canada).
† Adalat® XL® (nifedipine) 60 mg Tablets by Bayer Inc., Canada were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.
** Calculated using least-squares means

Summary of the comparative bioavailability data (60 mg fasted study):

Nifedipine 1 x 60 mg Extended-Release Tablets From measured data Uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEST Mylan-Nifedipine Extended Release* 60 mg Tablets	REFERENCE Adalat® XL® † 60 mg Tablets	% Ratio of Geometric Means**	90% Confidence Interval**
AUC_{0-t} (ng·h/mL)	859.1345 984.6623 (46.20)	834.2605 954.5187 (49.45)	103.0	94.95 – 111.69
AUC_{0-inf} (ng·h/mL)	871.2127 999.0401 (46.40)	844.8532 1057.6420 (46.33)	103.1	92.34 – 115.16
C_{max} (ng/mL)	38.2746 42.6485 (43.28)	32.5915 36.3091 (56.24)	117.4	108.13 – 127.54
T_{max}§	13.48 (51.92)	16.61 (57.68)		

Nifedipine 1 x 60 mg Extended-Release Tablets From measured data Uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEST Mylan-Nifedipine Extended Release* 60 mg Tablets	REFERENCE Adalat® XL® † 60 mg Tablets	% Ratio of Geometric Means**	90% Confidence Interval**
(h)				
$T_{½}$ § (h)	9.01 (43.44)	9.07 (32.17)		

* MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg Tablets (Manufactured by Schwarz, USA for Mylan Pharmaceuticals ULC, Canada).
† Adalat® XL® (nifedipine) 60 mg Tablets by Bayer Inc., Canada were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only.
** Calculated using least-squares means

Summary of the comparative bioavailability data (60 mg Multiple dose fasted study):

Nifedipine 1 x 60 mg Extended-Release Tablets, once daily, 5 days From measured data **Uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEST Mylan-Nifedipine Extended Release* 60 mg Tablets	REFERENCE Adalat® XL® † 60 mg Tablets	% Ratio of Geometric Means**	90% Confidence Interval**
AUC_{tau} (ng•h/mL)	810.0690 874.443 (42.013)	815.0902 898.931 (44.050)	99.4	92.1 – 107.2
C_{max} (ng/mL)	53.0754 56.242 (34.969)	54.5892 60.130 (43.958)	97.2	87.6 – 107.9
C_{min} (ng/mL)	17.1985 22.050 (69.661)	20.3305 24.287 (57.451)	84.6	72.8 – 98.3
T_{max} ¶ (h)	9.81 (49.308)	5.87 (68.670)		
FL¶ (%)	1.034 (46.875)	1.006 (40.337)		

* MYLAN-NIFEDIPINE EXTENDED RELEASE 60 mg Tablets (Manufactured by Schwarz, USA for Mylan Pharmaceuticals ULC, Canada).
† Adalat® XL® (nifedipine) 60 mg Tablets by Bayer Inc., Canada were purchased in Canada.
¶ Expressed as the arithmetic mean (CV%) only.
** Calculated using least-squares means

Summary of the comparative bioavailability data (30 mg single dose fasted study):

Nifedipine (1 x 30mg) Extended-Release Tablets From measured data **Uncorrected for potency** Geometric Least Squares Mean Arithmetic Mean (CV%)				
Parameter	TEST Mylan-Nifedipine Extended Release* 30 mg Tablets	REFERENCE Adalat® XL® † 30 mg Tablets	% Ratio of Geometric Least Squares Means	90% Confidence Interval
AUC_T (ng.h/mL)	488.196 610.398 (67.51)	498.626 699.988 (95.12)	97.91%	85.99% - 111.47%
AUC_I (ng.h/mL)	518.961 635.787 (65.29)	525.536 724.559 (92.87)	98.75%	86.68% - 112.50%
C_{max} (ng/mL)	26.893 32.174 (57.33)	25.770 31.547 (67.17)	104.36%	95.13% - 114.48%
T_{max}§ (h)	14.000 (5.00 - 32.00)	14.000 (4.00 - 28.00)		
$t_{½}$€ (h)	6.591 (42.51%)	6.673 (51.54%)		

* MYLAN-NIFEDIPINE EXTENDED RELEASE 30 mg Tablets (Manufactured by Schwarz, USA for Mylan Pharmaceuticals ULC, Canada).
† Adalat® XL® (nifedipine) 30 mg Tablets by Bayer Inc., Canada were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only

INSIGHT Trial

The International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment trial called INSIGHT was a prospective double-blind trial with dynamic randomization which enrolled mainly white hypertensive men and women. The primary endpoint was a composite of death from any cardiovascular or cerebrovascular cause, together with nonfatal stroke, myocardial infarction, and heart failure. The secondary endpoint included total mortality, death from a vascular cause, and non-fatal vascular events including transient ischemic attacks, angina (new or worsening), and renal failure. INSIGHT was designed to establish the superiority of nifedipine extended release tablets over the diuretic combination co-amilozide (hydrochlorothiazide and amiloride). When the results of the Swedish Trial in Old Patients with Hypertension-2 study (STOP-2) became known and because these results suggested that calcium-channel blockade and diuretic treatment had similar efficacy in preventing complications, but before the patient code in INSIGHT was broken, a secondary, noninferiority analysis was added.

INSIGHT randomized 6575 mild to moderate essential hypertensive or isolated systolic hypertensive patients, 55-80 years of age, with at least one other cardiovascular risk factor to nifedipine and co-amilozide. Patients were excluded if they had heart failure with low ejection fraction (<40%), unstable angina, PTCA (Percutaneous Transluminal Coronary Angioplasty) or

CABG (Coronary Artery Bypass Grafting) within 6 months prior to study start, or myocardial infarction or stroke in the 12 months prior to study start. Doses of each drug were titrated to achieve a target blood pressure of 140/90 mmHg (or drop of 20/10 mmHg) and if that target was not reached additional drugs could be added (atenolol and subsequently enalapril). On average patients were treated for 3.5 years. After placebo washout, the baseline blood pressure was 173/99 mmHg and decreased to 138/82 mmHg by the end of the trial in both groups. Heart rate was not different between the groups. At the end of the study, 69% and 72% of patients on nifedipine extended release tablets and hydrochlorothiazide/amiloride, respectively, were on monotherapy. All endpoints were assessed and adjudicated by the Critical Events Committee. The overall results of the study show that nifedipine extended release tablets were not inferior to the diuretic combination co-amilozide (see Table 5).

Table 5 – INSIGHT Trial Results

	Nifedipine Extended Release Tablets	Hydrochlorothiazide/ Amiloride	Odds Ratio (95% CI)	*P*-value
Primary Outcomes Composite	200 (6.3%)	182 (5.8%)	1.11 (0.90-1.36)	0.34
Secondary Outcomes Composite	383 (12.1%)	397 (12.5%)	0.96 (0.83-1.12)	0.62
Total Mortality	153 (4.8%)	152 (4.8%)	1.01 (0.80-1.27)	0.95
All Adverse Events	1546 (49%)	1327 (42%)	N/A	<0.001
Serious Adverse Events	796 (25%)	880 (28%)	N/A	0.02

DETAILED PHARMACOLOGY

Animal Pharmacology

In Vitro Animal Pharmacology

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.

In the cat papillary muscle under voltage clamp conditions, nifedipine at a concentration of 10^{-7} to 10^{-5} M did not influence the fast Na^{+} inward current, but depressed the slow Ca^{++} inward current in a dose-dependent manner without altering the kinetic control mechanism (gating mechanism).

In isolated rabbit ears perfused with tyrode solution, nifedipine has been shown to cause immediate vasodilation, loss of vascular tone and a lack of response to increases in perfusion pressure. However, subsequent neutralization of the drug effect could be achieved by an 8-fold increase in the extracelluar Ca^{++} concentration.

Studies in vitro using rat thoracic aorta and superior mesenteric artery preparations have shown that nifedipine inhibits contractions induced by potassium and noradrenaline. Tracing the movement of $^{45}Ca^{++}$ in these preparations showed that nifedipine 3×10^{-6} M reduced the calcium influx triggered by noradrenaline or depolarization. The influx could not be completely blocked and $^{45}Ca^{++}$ efflux remained unaffected.

Electrophysiologic Effect

In the isolated guinea-pig atria, the prolongation of the functional refractory period by nifedipine was not very pronounced, although there was a marked decrease in contractility. Even at high concentrations, nifedipine did not affect myocardial excitability.

In the conscious dog, nifedipine produced a moderate, dose-dependent PQ shortening. Only injection of large doses (0.3 to 30 µg) of nifedipine into the posterior septal artery induced a dose-dependent increase in AV conduction. The increase in blood flow through the posterior septal artery required only 1/10 of the dose necessary to affect AV conduction.

These electrophysiologic properties of nifedipine explain in part the lack of antiarrhythmic activity of the drug.

In Vivo Animal Pharmacology

Cardiovascular Effects

In dogs under opiate analgesia (thereby maintaining practically intact regulation of the circulation), nifedipine administered sublingually at dosages of 10-1000 µg/kg caused a dose-dependent increase in coronary flow, resulting in an increased oxygen supply to the heart. The peripheral flow, measured in the femoral artery, also increased in a dose-dependent manner. At low doses (10-31.5 µg/kg) the cardiac contractility, measured by left ventricular dp/dt, and the end-diastolic pressure were reduced or unaffected, while at higher doses (100-1000 µg/kg) there was an increase in dp/dt dependent on the increase in heart rate. Thus low doses of nifedipine may produce a negative inotropic effect, but higher doses produce greater peripheral vasodilation, and the direct negative inotropic effect is modified by the baroreceptor mediated reflex, positive inotropic response and tachycardia.

In further hemodynamic investigations conducted in conscious dogs with implanted aortic flow-probes, a reduction in total peripheral resistance was observed with nifedipine doses of only 10 µg/kg sublingually which did not appreciably lower the mean blood pressure. However, a decrease in the mean blood pressure occurred when doses were raised to 31.5 or 100 µg/kg. In the higher dose range there were significant decreases in peripheral resistance, with concomitant increases in heart rate, stroke volume and cardiac output as a result of compensatory mechanisms. The drop in peripheral resistance associated with the increase in cardiac output results in a partial transformation of the pressure workload of the heart into a volume workload which is considered to be less oxygen consuming. Lowering of the peripheral resistance also indicated that nifedipine reduces the afterload.

Antihypertensive Effects

In male spontaneously hypertensive rats, nifedipine was administered in single oral doses of 0.3, 1, 3, 6, or 9 mg/kg and compared to hydralazine 2.5, 6, or 7.5 mg/kg (5 animals/group). This was

followed by oral administration once a day for ten weeks of nifedipine 1, 3, 6, or 9 mg/kg/day or hydralazine 6 mg/kg/day (5-7 animals/group). No changes in blood pressure were seen after nifedipine 0.3 mg/kg but the 1 and 3 mg/kg doses caused maximal decrease in blood pressure 1-4 hours after administration. Maximal effects of the higher (6 and 9 mg/kg) doses of nifedipine were seen after 15 minutes with a slightly longer duration following 9 mg/kg. The hydralazine dose of 2.5 mg/kg was not observed to have an antihypertensive effect. Significant decreases in blood pressure were seen after 6 and 7.5 mg/kg with maximal effect after 2-4 hours. In the ten-week study, nifedipine at doses of 3 mg/kg/day and above produced significant decreases in blood pressure in the first week and throughout the subsequent weeks to the end of administration. The effect of nifedipine 9 mg/kg/day was comparable to that of hydralazine 6 mg/kg/day.

TOXICOLOGY

Acute Toxicity

Signs of toxicity were usually observed from 5 to 10 minutes after oral administration and immediately after intravenous administration. These include a reduction of spontaneous motility and apathy in association with increased frequency of respiration usually seen at the lower dosages, with saltatory and clonic spasm, cyanosis and death at the higher dosages. Post-mortem examinations revealed pulmonary edema in rats and cats.

Table 6 – LD_{50} in Animal Studies

Species	Dose Range (mg/kg)		LD_{50} (mg/kg)	
	Oral	Intravenous	Oral	Intravenous
Mouse	294 - 882	3 - 5	494 (421 - 572)	4.2 (3.8 - 4.6)
Rat	588 - 1323	10 - 25	1022 (950 - 1087)	15.5 (13.7 - 17.5)
Rabbit	100 - 500	1 - 4	250 - 500	2 - 3
Cat	50 - 250	0.5 - 8	100	0.5 - 8
Dog	250 - 2000	0.5 - 3	>250	2 - 3

Subacute Toxicity

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 thirteen weeks.

Carcinogenicity

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

In a two-year study, nifedipine was administered orally to male and female rats in the diet at doses of 5-9, 29-39, and 156-210 mg/kg/day. In the lowest dose group, nifedipine was without toxic effects. The higher doses led to dose-dependent, significant weight losses. An increased mortality was found in the 156-210 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 regard to tumorigenesis. Although the animals in the highest dose group showed no uncommon tumor incidence, this group was considered not suitable for comparison with the other treatment groups because of the high mortality rate. No significant differences were found between the controls and the remaining two groups with respect to the frequency, nature, and localization of tumors.

Reproductive 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 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 these animals.

Pre-natal 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 dosages 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.

Mutagenesis

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

In the Micronucleus test, two 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 12,500 µg per plate did not cause any bacteriotoxic 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.

REFERENCES

1. Banzet O., Colin J., Thibonier M., Siglas E., Alexandre J., Corvol P., Acute antihypertensive effect and pharmacokinetics of a tablet preparation of nifedipine. Eur. J. Clin. Pharmacol. 1983, 24:146-50.

2. Brennan F., Flanagan M., Blake S., Cannon P., Nifedipine in the treatment of hypertension. Eur. J. Clin. Pharmacol., 1983, 25: 713-5.

3. Bursztyn M., Grossman E., Rosenthal T., Long-acting nifedipine in moderate and severe hypertensive patients with serious concomitant diseases. Am Heart J. 1985, 110:96-101.

4. Erne P., Bolli P., Bertel O., Hulthen L., Kiowski W., Muller F.B., Buehler F., Factors influencing the hypotensive effects of calcium antagonists. Hypertension 1983, 5:II 97-102.

5. Fleckenstein, A.: Specific Pharmacology of Calcium in Myocardium, Cardiac Pacemakers and Vascular Smooth Muscle. Annu. Rev. Pharmacol. Toxcol. 1977; 17:149-166.

6. Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, et al. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013 Dec 18;310(23):2544-53.

7. Garthoff B., Kazda S., Knorr A., Thomas G., Factors involved in the antihypertensive action of calcium antagonists. Hypertension 1983, 5:II 34-38.

8. Gunther, et al: Inappropriate Coronary Vasoconstriction in Patients with Coronary Artery Disease: A Role for Nifedipine? Am. J. Cardiol. 1979; 44:793-797.

9. Hallin L., Andren L., Hansson L., Extended trial of nifedipine and bendroflumethiazide in hypertension., J. Cardiovasc. Pharmacol. 1983, 5:1083-5.

10. Halperin AK, Cubeddu L.X., The role of calcium channel blockers in the treatment of hypertension. Am. Heart J. 1986, 111: 363-82.

11. Hornung R.S., Gould B.A., Jones R.I., Sonecha T.N., Raftery E.B., Nifedipine tablets for systemic hypertension: a study using continuous ambulatory intraarterial recording. Am. J. Cardiol. 1983, 51:1323-7.

12. Jatene & Lichtlen, eds., 3rd Int. Adalat Symp., New Therapy of Ischemic Heart Disease. Amsterdam: Excerpta Medica, 1976.

13. Kenmure, A.C.F. and Scruton, J.H.: Double-blind Controlled Trial of the Anti-Anginal Efficacy of Nifedipine Compared with Propranolol. Br. J. Clin. Prac., 1979; 33(2): 49-51.

14. Kleinbloesem C.H., van Brummelen P., van der Linde J.A., Voogd P.J., Breimer D.D., Nifedipine: kinetics and dynamics in healthy subjects. Clin. Pharmacol. Ther. 1984, 35:742-9.

15. Landmark K., Antihypertensive and metabolic effects of long-term therapy with nifedipine slow-release tablets. J. Cardiovasc. Pharmacol. 1985, 7:12-7.

16. Lochner W., Braasch W., Kroneberg, G. eds., 2nd Int. Adalat Symp., New Therapy of Ischemic Heart Disease. New York: Springer-Verlag, 1975.

17. Lund-Johansen P., Omvik P., Hemodynamic effects of nifedipine in essential hypertension at rest and during exercise. J. Hypertension 1983, 1:159-63.

18. Moskowitz, et al: Nifedipine Therapy for Stable Angina Pectoris. Preliminary Results of Effects on Angina Frequency and Treadmill Exercise Response. Am. J. Cardiol. 1979; 44:811-816.

19. Myers M.G., Leenen F.H.H., Burns R., Frankel D., Nifedipine tablets versus hydralazine in patients with persisting hypertension who receive combined diuretic and beta blocker therapy. Clin. Pharmacol. Ther. 1986, 398:409-13.

20. Ochs H.R., Ramsch K.D., Verburg-Ochs B., Greenblatt D.J., Gerloff J., Nifedipine, Kinetics and Dynamics after Single Oral Doses. Klin Wochenschr. 1984, 62:427-29.

21. Oehman K.P., Weiner L., von Schenck H., Karlberg B.E., Antihypertensive and metabolic effects of nifedipine and labetalol alone and in combination in primary hypertension. Eur. J. Clin. Pharmacol. 1985, 29:149-54.

22. Puech and Krebs, eds., 4th Int. Adalat Symp., New Therapy of Ischemic Heart Disease. Amsterdam: Excerpta Medica, 1980.

23. Rowland, et al: Effect of Nifedipine on Atrial Ventricular Conduction as Compared with Verapamil. Br. H.J. 1979; 42:124-127.

24. Sorkin E.M., Clissold S.P., Brogden R.N., Nifedipine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related disorders Drugs 1985, 30:182-274.

25. Swanson D.R., Barclay B.L., Wong, P.S.L., Theeuwes F., Nifedipine Gastrointestinal Therapeutic System. The American Journal of Medicine, 1987; 83 (6B): 3-9.

26. Toal, C.B. Efficacy of a low dose nifedipine GITS (20 mg) in patients with mild to moderate hypertension. Canadian Journal of Cardiology, 1997; 13 (10): 921-927.

27. ADALAT® XL®, Bayer Inc., Product Monograph dated: July 25, 2016, Control No.: 194331.

PART III: CONSUMER INFORMATION

[Pr] MYLAN-NIFEDIPINE EXTENDED RELEASE

Nifedipine Extended Release Tablets

20 mg, 30 mg and 60 mg

USP

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-NIFEDIPINE EXTENDED RELEASE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MYLAN-NIFEDIPINE EXTENDED RELEASE is used for:

Chronic Stable Angina

MYLAN-NIFEDIPINE EXTENDED RELEASE may be used in patients to manage chronic stable angina.

High Blood Pressure

MYLAN-NIFEDIPINE EXTENDED RELEASE may be used in patients to manage mild to moderate high blood pressure.

What it does:

MYLAN-NIFEDIPINE EXTENDED RELEASE manages high blood pressure and chronic stable angina. It is called a "calcium channel blocker". Although the mechanism by which MYLAN-NIFEDIPINE EXTENDED RELEASE reduces blood pressure and relieves angina is not fully known, it is believed to be brought about as a result of the ability of MYLAN-NIFEDIPINE EXTENDED RELEASE to widen and relax blood vessels.

When it should not be used:

You should not use MYLAN-NIFEDIPINE EXTENDED RELEASE if you:

- are allergic to nifedipine, or to any of the nonmedicinal ingredients
- have allergies to other drugs that are similar to MYLAN-NIFEDIPINE EXTENDED RELEASE (dihydropyridines calcium antagonists)
- are pregnant, breastfeeding, or a woman of childbearing age
- have severe low blood pressure or are in shock
- are taking the medicine rifampicin
- have a Kock pouch (a pouch or reservoir created inside the abdomen with a portion of large bowel for which a tube or catheter can be inserted through the abdominal wall to drain the reservoir)
- have moderate to severe liver disease
- have severe narrowing in your stomach or intestines

What the medicinal ingredient is:

Nifedipine.

What the non-medicinal ingredients are:

20 mg: cellulose acetate, colloidal silicon dioxide, FD&C Blue #1, hydroxypropylcellulose, hydroxypropyl methylcellulose, iron oxide black, iron oxide red, magnesium stearate, polydextrose, polyethylene glycol, polyethylene oxide, propylene glycolsodium chloride, sodium stearyl fumarate and titanium dioxide.

30 mg and 60 mg: Cellulose acetate, colloidal silicon dioxide, glycerol triacetate, hydroxypropyl methylcellulose, iron oxide black, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate, povidone, propylene glycol, sodium chloride and titanium dioxide.

What dosage forms it comes in:

The medication in MYLAN-NIFEDIPINE EXTENDED RELEASE is packed within a nonabsorbable shell that has been specially designed to slowly release the drug at a constant rate over time so that the body can absorb it. The shell will pass into your stool after your body has

absorbed the medicine. This is normal and is nothing to worry about.

MYLAN-NIFEDIPINE EXTENDED RELEASE 20 mg are available in bottles of 30 tablets and 100 tablets and cartons with blisters of 30 tablets (3x10's).

MYLAN-NIFEDIPINE EXTENDED RELEASE 30 mg and 60 mg are available in bottles of 100 tablets and cartons with blisters of 30 tablets (2x15's).

WARNINGS AND PRECAUTIONS

Before you use MYLAN-NIFEDIPINE EXTENDED RELEASE, talk to your doctor or pharmacist if you:

- are pregnant or breastfeeding
- have heart failure, liver disease, kidney disease, or coronary artery disease
- have unstable angina (sudden chest pain that occurs at rest and gets increasingly worse)
- have recently had a heart attack or you have a heart condition called aortic stenosis (narrowing of a valve in your heart)
- have pre-existing gastrointestinal narrowing disease
- have diabetes
- have a history of poor blood circulation in the brain.
- are scheduled for surgery with a general anaesthetic
- are a man and have been repeatedly unsuccessful at fathering a child by in vitro fertilization

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to MYLAN-NIFEDIPINE EXTENDED RELEASE. Your ability to drive or to operate machinery may be impaired particularly at the start of treatment, when changing the medication, or in combination with alcohol.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your healthcare professional about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with MYLAN-NIFEDIPINE EXTENDED RELEASE:

Drug-Drug Interactions

- azole antifungals (ketoconazole, itraconazole or fluconazole
- cyclosporine
- carbamazepine
- cimetidine, ranitidine
- diltiazem
- digoxin
- erythromycin, clarithromycin
- fluoxetine
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, or amprenavir)
- nefazodone
- phenobarbital
- phenytoin
- quinidine
- quinupristin/dalfopristin
- tacrolimus
- rifampicin
- valproic acid
- blood pressure lowering drugs including beta blockers
- benzodiazepines
- cisapride
- coumarin anticoagulants
- warfarin
- imipramine
- propafenone
- terfenadine

Drug-Food Interactions

DO NOT eat grapefruit or drink grapefruit juice while you are using this medicine.

Drug-Herb Interactions

Saint John's Wort

PROPER USE OF THIS MEDICATION

You must swallow MYLAN-NIFEDIPINE EXTENDED RELEASE tablets whole. Do not bite, chew, divide or crush the tablets. This can result in a large immediate release of the drug.

You can take this medication with or without food.

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Follow your doctor's treatment plan exactly so that you reach and maintain your blood pressure targets, and get relief from angina. Do not use more medicine or use it more often than your doctor tells you to.

Do not discontinue a medication on your own. If you have a problem with a drug, always tell your doctor.

Dosage should be individualised.

Usual dose:

Doses greater than 90 mg a day are not recommended.

Chronic Stable Angina

- Starting Dose: 30 mg once a day

High Blood Pressure

- Starting Dose: 20 mg to 30 mg once a day
- Usual Maintenance Dose: 30 to 60 mg once a day.

Overdose

If you think you have taken too much MYLAN-NIFEDIPINE EXTENDED RELEASE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose unless instructed by your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- headaches, anxiety, numbness and/or pins and needles (hypoesthesia), confusion, insomnia, nervousness, weakness, excessive muscle movement
- dizziness, fatigue
- nausea, upset stomach, indigestion, dry mouth
- enlargement of the gums
- muscle or joint pain, leg cramps, back pain
- rash, itch, sensitivity to the sun
- impotence, breast enlargement in men, menstrual disorder for women
- abnormally large production of urine, the need to urinate at night, lack of urine or incontinence
- eye pain

If any of these affects you severely, tell your doctor, nurse or pharmacist.

MYLAN-NIFEDIPINE EXTENDED RELEASE can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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	Wheezing or trouble breathing			√
	Angina Pectoris: chest tightness, chest pain			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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	
	Edema: swelling of tissues of the hands, ankles, feet or legs	√		
	Abdominal cramps		√	
	Vomiting		√	
	Diarrhea		√	
	Irregular heartbeat			√
	Fast heartbeat			√
Uncommon	Constipation		√	
	Allergic Reactions: 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			√
	Low Blood Pressure: dizziness, fainting, lightheadedness		√	
Unknown	**Liver Disorder (hepatitis and cholestasis):** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Myocardial Infarction:			√
	heart attack			
	Toxic Epidermal Necrolysis: severe skin peeling, especially in the mouth and eyes			√
	Intestinal (bowel) Obstruction: swollen, hard or painful abdomen, vomiting, and constipation/no stools.			√

This is not a complete list of side effects. For any unexpected side effects while taking MYLAN-NIFEDIPINE EXTENDED RELEASE, contact your doctor or pharmacist.

HOW TO STORE IT

MYLAN-NIFEDIPINE EXTENDED RELEASE 20 mg, 30 mg and 60 mg should be stored between 15°C and 30°C. Protect from light, humidity and moisture.

Keep out of reach and sight of children.

Never share your medicine with anyone.

Ask your healthcare professional about the best way to dispose of any outdated medicine or medicine no longer needed.

IMPORTANT: PLEASE READ

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

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC, Etobicoke, Ontario M8Z 2S6.

Date of revision: December 22, 2017

Mylan

Mylan Pharmaceuticals ULC
Etobicoke, ON M8Z 2S6
1-800-575-1379
www.mylan.ca