

**PRODUCT MONOGRAPH**

**N I F E D I P I N E**

**Nifedipine Capsules USP**

**5 a n d 1 0 m g**

**Anti-Anginal Agent**

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## **PRODUCT MONOGRAPH**

NIFEDIPINE

Nifedipine Capsules USP

5 and 10 mg

### **THERAPEUTIC CLASSIFICATION**

Anti-anginal agent

### **ACTION AND CLINICAL PHARMACOLOGY**

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.

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.

### Pharmacokinetics

In man, oral administration of 10 mg C<sup>14</sup> 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 ( $t_{1/2\beta}$ ) of 2.5 to 3 hours and a terminal slow half-life ( $t_{1/2\alpha}$ ) of 5 hours.

Studies in man, 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%. The acid form is mainly excreted in the urine. Protein binding of circulating nifedipine exceeds 90%.

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

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). In these patients, there is a considerable risk of accumulation (see PRECAUTIONS).

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 PRECAUTIONS – Interaction with Grapefruit Juice).

#### Comparative Bioavailability

A comparative bioavailability study was performed on Adalat 10 mg capsules vs. NIFEDIPINE 10 mg capsules using 24 (twenty-four) normal volunteers. A single dose of 20 mg was

administered. The results are as follows:

	<u>Adalat</u>	<u>NIFEDIPINE</u>
AUC <sub>0-18</sub> (ng-hrs/mL)	302	287
C <sub>max</sub> (ng/mL)	200	193
T <sub>max</sub> (hrs)	0.60	0.62

### **INDICATIONS AND CLINICAL USE**

1. NIFEDIPINE (nifedipine) may be used in the management of angina resulting from coronary artery spasm.
2. NIFEDIPINE is indicated for 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 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 WARNINGS).

## **CONTRAINDICATIONS**

NIFEDIPINE (nifedipine) is contraindicated in pregnancy, during lactation and in women of child-bearing 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.

In patients with acute myocardial infarction (see WARNINGS – Patients with Myocardial Infarction).

In patients with cardiovascular shock.

In patients with hypersensitivity to nifedipine.

In patients with severe hypotension.

## **WARNINGS**

NIFEDIPINE (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. Occasional 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 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.

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. 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.

## **PRECAUTIONS**

### **Hypotension**

Because NIFEDIPINE (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 observation 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).

### **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 ADVERSE REACTIONS). 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.

### **Use in Elderly**

Nifedipine should be administered cautiously to elderly patients, especially to those with a history of hypotension or cerebral vascular insufficiency. (See DOSAGE AND ADMINISTRATION).

### Use in Diabetic Patients

The use of nifedipine in diabetic patients may require adjustment of their control.

### Use in Patients with Impaired Liver Function

Nifedipine should be used with caution in patients with impaired liver function (see CLINICAL PHARMACOLOGY). A dose reduction, particularly in severe cases, may be required. The response and metabolic effect should be monitored closely.

### 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 ACTION AND CLINICAL PHARMACOLOGY — Pharmacokinetics). Therefore, consumption of grapefruit juice prior to or during treatment with nifedipine should be avoided.

### Drug Interactions

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.

Drugs known to be inhibitors of the cytochrome P450 system include azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine and warfarin.

Drugs known to be inducers of the cytochrome P450 system include phenobarbital, phenytoin and rifampin.

Drugs known to be biotransformed via P450 include benzodiazepines, flecainide, imipramine, propafenone and theophylline.

The antihypertensive effect of beta-blockers may be augmented by nifedipine's reduction of peripheral vascular resistance. The concomitant administration of nifedipine with beta-adrenergic blocking drugs warrants caution and careful monitoring of the blood pressure and pulmonary signs and symptoms of congestive failure (see WARNINGS).

Long acting nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Antihypertensives: Nifedipine may potentiate the effects of hypotensive agents.

Concomitant use of nifedipine with short-acting nitrates, furosemide and anticoagulants has shown no interaction or unusual toxic effects.

Administration of nifedipine with digoxin may lead to reduced digoxin clearance, and therefore, an increase in the plasma digoxin level. It is recommended that the digoxin levels be monitored when

initiating, adjusting and discontinuing nifedipine to avoid possible under- or over-dosing with digitalis.

The addition of nifedipine to a stable quinidine regimen may reduce the quinidine concentration 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. Therefore, 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.

Pharmacokinetic studies have shown that concurrent administration of cimetidine or ranitidine and 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.

### **ADVERSE REACTIONS**

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.

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%).

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:

#### Cardiovascular

Peripheral edema, fluid retention and swelling:	8.3%
Flushing, heat sensation:	7.4%
Hypotension:	3.5%
Palpitation and increased heart rate:	2.6%
Syncope:	0.4%

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, lightheadedness, giddiness:	11.9%
Headache:	7.8%
General weakness:	6.3%
Shakiness, nervousness and jitteriness:	1.9%
Sleep disturbances:	1.1%
Blurred vision:	0.9%
Depression:	0.6%

### Gastrointestinal

Nausea and vomiting:	6.4%
Abdominal discomfort and heartburn	2.0%
Diarrhoea:	0.9%
Constipation:	0.6%

### Musculoskeletal

Joint stiffness, muscle pain and cramps:	4.3%
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### Respiratory Tract

Shortness of breath, dyspnea:	1.3%
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Nasal congestion: 0.5%

Others

Pruritus, dermatitis, urticaria and rash: 1.9%

Fever, sweating and chills: 1.4%

Two cases of hypersensitivity have been reported resulting in an allergic hepatitis which resolved when the drug was discontinued. In one case, recurrence was observed on re-challenge.

Nifedipine has been reported to cause in a small number of patients gingival hyperplasia similar to that caused by diphenylhydantoin. The lesions usually regressed on discontinuation of nifedipine. However, on occasion, gingivectomy was necessary.

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

One case of anaphylactic reaction has been reported.

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

Laboratory Tests

Rarely, mild to moderate transient elevations of enzymes such as alkaline phosphatase, CPK, LDH,

SGOT and 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 BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency taking nifedipine.

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There are several well documented cases of nifedipine immediate-release overdose. 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 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. Haemodialysis 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 overdose. Appropriate clinical measures, according to the nature and severity of the symptoms, should be applied.

## **DOSAGE AND ADMINISTRATION**

In all cases, dosage should be adjusted to individual patient requirements.

The starting dose of NIFEDIPINE (nifedipine) is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective dose range is 10-20 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 20-30 mg three or four times daily may be effective. A maximum daily dose of 120 mg may be used.

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.

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

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

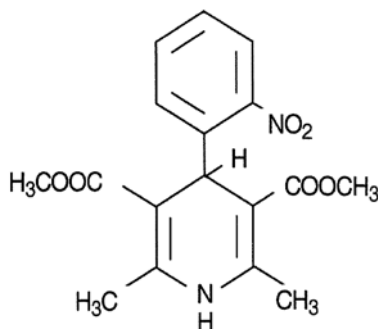
### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper/Common Name: nifedipine

Chemical Name: 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester

Structural Formula:



Molecular Formula: C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>

Molecular Weight: 346.3

Description: 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.

#### Stability and Storage Recommendations

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

### **AVAILABILITY OF DOSAGE FORMS**

NIFEDIPINE (nifedipine) 5 mg: each mustard-coloured, opaque, soft gelatin capsule, imprinted '5', contains nifedipine 5 mg. Available in bottle of 100.

NIFEDIPINE (nifedipine) 10 mg: each mustard-coloured, opaque, soft gelatin capsule, imprinted '10', contains nifedipine 10 mg. Available in bottle of 100.

### **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  $10^{-5}$  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's ear perfused with Tyrode solution, nifedipine has been shown to cause immediate vasodilation, loss of vascular tone and irresponsiveness to increased in perfusion pressure.

However, subsequent neutralization of the drug effect could be achieved by an 8-fold increase in

the extracellular  $\text{Ca}^{++}$  concentration.

### Cardiovascular Effects

In a study employing the isolated guinea pig heart, nifedipine strongly increased coronary perfusion even at low concentrations of  $10^{-9}$  to  $10^{-8}$  g/mL. There was also a dose-dependent decrease in oxygen consumption, left ventricular systolic pressure, and the maximum rate of pressure increase in the left ventricle (dp/dt). The basic effects on the isolated hearts are therefore an increase in myocardial perfusion, negative inotropic effect, and a consequent decrease in oxygen consumption of the cardiac muscle.

In dogs under opiate analgesia (thereby maintaining practically intact regulation of the circulation), nifedipine administered sublingually at dosages of 10 - 1000  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$ ) the cardiac contractility, measured by left ventricular dp/dt, and the end-diastolic pressure were reduced or unaffected, while at higher doses (100 - 1000  $\mu\text{g}/\text{kg}$ ) 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  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$ . In this 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 indicates that nifedipine reduces the afterload.

### Electrophysiologic Effects

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 by injection of large doses (up to 30  $\mu\text{g}$ ) of nifedipine into the posterior septal artery did a dose-dependent increase in A-V conduction occur. The increase in blood flow through the posterior septal artery required only 1/10 the dose necessary to affect A-V conduction.

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

## TOXICOLOGY

### Acute Toxicity Studies

<u>Animal Species</u>	<u>Sex</u>	<u>Dose Level (mg/kg)</u> oral administration	<u>LD<sub>50</sub> mg/kg</u>
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

The oral LD<sub>50</sub> 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.

#### Chronic Toxicity and Carcinogenicity Studies

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 5-9, 29-39, and 156-210 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 156-210 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 localisation of tumors.

#### 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 ug 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.

### Reproduction Studies

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.

## BIBLIOGRAPHY

1. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm. *N Eng J Med* 1980; 302: 1269-1273.
2. Ebner F, Dunschede HB. Haemodynamics, therapeutic mechanism of action and clinical findings of Adalat use based on worldwide clinical trials. In: Jatene AD, Lichtlen PR, eds. *New therapy of ischemic heart disease. Third Int Adalat Symp. Amsterdam Excerpta Medica, 1976; 283-300.*
3. Fleckenstein A. On the basic pharmacological mechanism of nifedipine and its relation to therapeutic efficacy. In: Jatene AD, Lichtlen PR, eds. *New therapy of ischemic heart disease. Third Int Adalat Symp. Amsterdam Excerpta Medica, 1976; 1-13.*
4. Goldberg S, Reichek N, Wilson J, et al. Nifedipine in the treatment of Prinzmetal's (variant) angina. *Am J Cardiol* 1979; 44: 804-810.
5. Gunther S, Green L, Muller JE, et al. Inappropriate coronary vasoconstriction in patients with coronary artery disease: a role for nifedipine? *Am J Cardiol* 1979; 44: 793-797.
6. Heupler FA Jr., Proudfit WL. Nifedipine therapy for refractory coronary arterial spasm. *Am J Cardiol* 1979; 44: 798-803.
7. Kenmure ACF, Scruton JH. A double-blind controlled trial of the anti-anginal efficacy of nifedipine compared with propranolol. *Br J Clin Pract* 1979; 33: 49-51
8. Maseri AM, L'Abbate A, Chierchia S, et al. Significance of spasm in the pathogenesis of ischemic heart disease. *Am J Cardiol* 1979; 44: 788-792.
9. Moskowitz RM, Piccini PA, Nacarelli GV, Zelis R. Nifedipine therapy for stable angina pectoris: preliminary results of effects on angina frequency and treadmill exercise response. *Am J Cardiol* 1979; 44: 811-816.
10. Mueller HS, Chahine RA. Interim report of multicenter double-blind placebo-controlled studies of nifedipine in chronic stable angina. 1981; 71: 645-657.
11. Rowland E, Evans T, Krikler D. Effect of nifedipine on atrioventricular conduction as compared with verapamil. Intracardiac electrophysiological study. *Br Hert J* 1979; 42: 124-127.
12. Sherman LG, Liang C-S. Nifedipine in chronic stable angina: a double-blind placebo-controlled crossover trial. *Am J Cardiol* 1983; 51: 706-711.
13. Stone PH, Muller JE, Turi ZG, et al. Efficacy of nifedipine therapy in patients with refractory angina pectoris: significance of the presence of coronary spasm. *Am Heart J* 1983; 106: 644-

652.

14. Terry RW. Nifedipine therapy in angina pectoris: evaluation of safety and side effects. *Am Heart J* 1982; 104: 681-689.

15. Adalat Summary Basis of Approval, FDA.