NIFEdipine Extended-Release Tablets, USP

For Oral Use

DESCRIPTION

NIFEdipine is a drug belonging to a class of pharmaceutical agents known as the calcium channel blockers. It acts on the smooth muscle of blood vessels to decrease the peripheral resistance and peripheral vascular resistance.

INDICATIONS AND USAGE

I. Vasospastic Angina

NIFEdipine extended-release tablets are indicated for the management of stable angina pectoris associated with exertional angina in patients whose angina is either not effectively controlled by the use of propranolol or who are intolerant of the drug.

II. Hypertension

NIFEdipine extended-release tablets are indicated for the treatment of hypertension in patients who are receiving one or more antihypertensive agents and who have not responded adequately to any combination of these agents.

Mechanism of Action

A) Angina

The primary mechanism by which inhibition of calcium influx relaxes angina has not been fully determined, but includes at least the following two mechanisms:

1) Decrease in myofilament sensitivity to calcium

NIFEdipine dilates the coronary arteries in the intact vascular smooth muscle. This effect is probably the result of a decrease in cytosolic free calcium.

2) Reduction of Oxygen Utilization

NIFEdipine reduces oxygen demand by decreasing myocardial contractility and the oxygen requirements of the heart muscle. This effect is achieved by a decrease in left ventricular filling pressure and an increase in ejection fraction and reduction in left ventricular filling pressure.

B) Hypertension

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and the resulting reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an imbalance of vasodilator and vasoconstrictor responses.

NIFEdipine selectively inhibits calcium ions across the cell membrane and the arterial smooth muscle, and thereby reduces the arterial wall tension and pressure.

Pharmacokinetics and Metabolism

NIFEdipine is completely absorbed after oral administration. Plasma drug concentrations rise at a slower rate and control a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of absorption and a prolonged control rate of 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Other adverse reactions were reported sporadically with an incidence of 1% or less. These include:
- Body as a Whole: Edema, flushing, pain, rash
- Cardiovascular: Angina, hypertension, tachycardia, syncope
- Central Nervous System: Anxiety, ataxia, decreased libido, depression, dizziness, hypotension, hyperesthesia, migraine, paresthesia, tremor
- Dermatologic: Eruptions, increased sweating, urticaria, purpura
- Gastrointestinal: Nausea, vomiting, constipation, diarrhea, dyspepsia, melena
- General: Fatigue, back pain, gout, myalgia
- Respiratory: Coughing, epistaxis, upper respiratory tract infection, respiratory disorder, rhinitis
- Other: Abnormal lacrimation, abnormal vision, taste perversion, limbitus

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications. The following adverse experience, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is not established:

- General: Generalized fluid retention

In addition, more serious adverse events were 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. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias and atrial fibrillation have also been reported.

The usual side effects that accompany the administration of calcium channel blockers are rare but generally do not limit therapy. The most common side effect reported is generalized fluid retention. With patients whose angina or hypertension is complicated by generalized fluid retention, digitalization may be required.

Cases of tablet adherence to the gastrointestinal wall with ulceration have been reported, some requiring hospitalization and intervention.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported sporadically, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of nifedipine.

### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Nifedipine Capsules (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Tiredness</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Muscle cramps, tremor</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Nervousness, mood</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Flushing, cold sweat</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea, cough, wheezing</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Nasal congestion, sore throat</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

There is also a large uncontrolled experience in over 2100 patients in the United States. Most patients had vasospastic or resistant angina, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with nifedipine extended-release tablets.

In addition, more serious adverse events were 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. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias and atrial fibrillation have also been reported.

In a subgroup of over 1000 patients receiving nifedipine with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of nifedipine-treated patients.

### Pharmacokinetics and Metabolism

Nifedipine is metabolized by CYP3A4. Coadministration of nifedipine with phenytoin, an inducer of CYP3A4, resulted in a doubling in nifedipine AUC and Cmax with no change in half-life. The increased plasma drug bioavailability may be attributed to a decrease in the extent of first-pass metabolism of nifedipine. A similar effect has been observed with nifedipine extended-release tablets.

Markedly reduced gastrointestinal transit time over prolonged periods may occur with nifedipine extended-release tablets. Cases of bezoars have been reported in association with nifedipine extended-release tablets, even in patients with no prior history of gastrointestinal disease. (See WARNINGS)

### Drug Interactions

### Other Interactions

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients with hypertension than in white patients. Since the blood pressure-lowering effects of nifedipine are moderate, black patients with hypertension may require higher doses than white patients.

### Dosage and Administration

Doseage must be adjusted according to each patient's needs. Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily. Nifedipine Extended-Release Tablets: For the treatment of angina, titration should proceed over a 7 to 14 day period so that the physician can fully assess the response to each dose level and monitor blood pressure before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, titration may proceed more rapidly if symptoms are well controlled and the patient is assessed frequently. If angina is severe or if angina is increased, more rapid titration of intravenous nifedipine is recommended. If angina is increased, it is recommended to continue angina and Nifedipine Extended-Release Tablets should be initiated with 30 mg once daily. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. Experience with doses greater than 90 mg in patients with angina is limited. Therefore, doses greater than 90 mg should be used with caution and only when clinically warranted.

Avoid coadministration of nifedipine and grapefruit juice (see CLINICAL PHARMACOLOGY and PRECAUTIONS: Other Interactions). No “ceiling effect” has been observed upon discontinuation of nifedipine extended-release tablets. However, if discontinuation of nifedipine is necessary, slow wound practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing nifedipine extended-release tablets to assure that the extended release dosage form has been prescribed.

Coadministration with Other Antihypertensive Drugs Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See PRECAUTIONS: Drug Interactions, for information on coadministration of nifedipine with beta blockers or long-acting nitrates.

**HOW SUPPLIED**

Nifedipine Extended-Release Tablets, USP are supplied as 30 mg round, biconvex, rose-pink, film-coated tablets with “T010” in black ink on one side and plain on the other side:

- Bottles of 100 (NDC 24979-011-01)
- Bottles of 30 (NDC 24979-011-12)

Nifedipine Extended-Release Tablets, USP are supplied as 60 mg round, biconvex, rose-pink, film-coated tablets with “T010” in black ink on one side and plain on the other side:

- Bottles of 100 (NDC 24979-010-01)
- Bottles of 30 (NDC 24979-010-12)

Nifedipine Extended-Release Tablets, USP are supplied as 90 mg round, biconvex, rose-pink, film-coated tablets with “T010” in black ink on one side and plain on the other side:

- Bottles of 100 (NDC 24979-009-01)
- Bottles of 30 (NDC 24979-009-12)

Store at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature] Protect from moisture and humidity.

Manufactured by:

- TWPharmaceutical USA, Inc.
- Paramus, NJ 07652

Produced by:

- China Chemical & Pharmaceutical Co., Ltd.
- Tainan City, 72042, Taiwan

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