**ISOSORBIDE MONONITRATE EXTENDED-RELEASE TABLETS USP** 30 mg, 60 mg, and 120 mg.

**DESCRIPTION**
Isosorbide mononitrate (ISMN), an organic nitrate and the major biologically active metabolite of isosorbide dinitrate, is a vasodilator with effects on both arterioles and veins. Isosorbide mononitrate extended-release Tablets, for oral administration, contain either 30 mg, 60 mg or 120 mg of isosorbide mononitrate extended-release tablets once daily, taken early in the morning on arising, provided at least 12 hours of antanginal activity.

In a placebo-controlled parallel study, 30, 60, 120 and 240 mg of isosorbide mononitrate extended-release tablets were administered once daily for up to 6 weeks. Prior to randomization, all patients completed a 1- to 3-week, single-blind placebo course to demonstrate nitrate responsiveness and total exercise treadmill time reproducibility. Exercise-tolerance tests using the Bruce Protocol were conducted prior to and at 4 and 12 hours after the morning dose on days 1, 7, 14, 28 and 42 of the double-blind period. Isosorbide mononitrate extended-release tablets 30 and 60 mg (only doses evaluated acutely) demonstrated a significant increase from baseline in total treadmill time relative to placebo at 4 and 12 hours after the administration of the first dose. At day 42, the 120 and 240 mg dose of isosorbide mononitrate extended-release tablets demonstrated a significant increase in total treadmill time at 4 and 12 hours post dose and at day 42. At 30 and 60 mg dose it could no longer be differentiated from placebo. Throughout chronic dosing, rebound was not observed in any isosorbide mononitrate extended-release tablets treatment group.

**Food Effects**
The influence of food on the bioavailability of ISMN after single-dose administration of isosorbide mononitrate extended-release tablets 30 mg to 60 mg was evaluated in three different studies involving either a “light” breakfast or a high-calorie, high-fat breakfast. Results of these studies indicate that concomitant food intake may decrease the rate (increase in Tmax) but not the extent (AUC) of absorption of ISMN.

**CLINICAL TRIALS**
Controlled trials with isosorbide mononitrate extended-release tablets have demonstrated antanginal activity following acute and chronic dosing. Administration of isosorbide mononitrate extended-release tablets once daily, taken early in the morning on arising, provided at least 12 hours of antanginal activity.

**WARNINGS**
Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. The importance of these observations to the routine, clinical use of oral isosorbide mononitrate is not known.

**INFORMATION FOR PATIENTS**
Patients should be told that the antanginal efficacy of isosorbide mononitrate extended-release tablets by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been established. As with other nitrates, daily headaches sometimes accompany treatment with isosorbide mononitrate. The patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with isosorbide mononitrate, since loss of headaches may be associated with simultaneous loss of antanginal efficacy. Administration of a calcium channel blocker often effectively relieves isosorbide mononitrate-induced headaches with no deleterious effect on isosorbide mononitrate’s antanginal efficacy.

**Drug Interactions**
The vasodilating effects of isosorbide mononitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

**CAUTION**
caution due to the small number of subjects in each age subgroup and consequently the lack of sufficient statistical power.

The following table summarizes key pharmacokinetic parameters of ISMN after single- and multiple-dose administration of ISMN as an oral solution or isosorbide mononitrate extended-release tablets:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Tmax (hr)</th>
<th>AU C (ng•hr/mL)</th>
<th>Cl/F (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISMN 60 mg</td>
<td>Single-dose studies</td>
<td>4.8-5.1</td>
<td>1424-1534</td>
<td>124-122</td>
</tr>
<tr>
<td>ISMN 60 mg</td>
<td>Multiple-dose studies</td>
<td>6.3-6.6</td>
<td>5990-7452</td>
<td>131-187</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**
Concentrations that are continuously greater than a minimally effective concentration. This concentration is achieved in a few minutes (9-13 min) after oral administration of a 5 mg dose and is maintained for at least 5-6 hours. Pooled data from two other trials, comparing isosorbide mononitrate extended-release tablets 30 mg once daily, ISDN 30 mg GID, and placebo GID in patients with chronic stable angina using a randomized, double-blind, three-way crossover design found statistically significant increases in exercise tolerance times for isosorbide mononitrate extended-release tablets compared to placebo at hours 4, 8 and 12 and to ISDN at hour 4. The increases in exercise tolerance on day 14, although statistically significant compared to placebo, were about half of that seen on day 1 of the trial.

**INDICATIONS AND USAGE**
Isosorbide mononitrate extended-release tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of oral isosorbide mononitrate is not sufficient for this product to be useful in aborting an acute anginal episode.

**CONTRAINDICATIONS**
Isosorbide mononitrate extended-release tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrates.
Drug/Laboratory Test Interactions
Nitrate and nitrites may interfere with the Zielo-Zak color reaction, causing falsely low readings in serum cholesterol determinations.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was observed in rats exposed to isosorbide mononitrate in their diets at doses of up to 900 mg/kg/day for the first 6 months and 500 mg/kg/day for the remainder of a 2-year study. In mice dosed for up to 121 weeks and females were dosed for up to 137 weeks. No evidence of carcinogenicity was observed in mice exposed to isosorbide mononitrate in their diets for up to 104 weeks at doses of up to 900 mg/kg/day, but tumors were observed in the noncarcinogenic tissues of 18% of the animals. Isosorbide mononitrate did not produce gene mutations (Ames test, mouse lymphoma test) or chromosome aberrations (human lymphocyte and mouse micronutests) at biologically relevant concentrations.

No effects on fertility were observed in a study in which male and female rats were administered dosages of up to 1750 mg/kg/day in males, in the rat. In males, sperm morphology was not affected in the highest dose group when compared to controls. In female rats, administration of isosorbide mononitrate at 40 mg/kg/day to pregnant rats did not affect fertility through pregnancy and lactation. In addition, the three North American trials were pooled with 11 controlled trials conducted in Europe. Among the 14 controlled trials, a total of 711 patients were randomized to isosorbide mononitrate extended-release tablets. When the pooled data were reviewed, headache and dizziness were the most common adverse events that were reported by ≥5% of patients. Other adverse events, each reported by ≤5% of exposed patients, and in many cases of uncertain relation to drug treatment were:

Vertigo, dizziness, syncope, hypotension, syncope, taste perversion, visual disturbances.

OVERDOSAGE
Cardiotoxic Effects
The ill effects of isosorbide mononitrate overdose are generally the result of isosorbide mononitrate's pharmacology on blood pressure. Because the dosages of isosorbide mononitrate that might cause methemoglobinemia are larger than those that result in methemoglobinemia, it is likely that the clinical effects of isosorbide mononitrate overdose will be less severe. Methemoglobinemia is not a cause of death. However, because of the severity of the clinical effects, patients with isosorbide mononitrate overdose should be considered toxicologically unstable.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide mononitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Mechemoglobinemia
Mechemoglobinemia has been reported in patients receiving other organic nitrates, and it is probably also occurred as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b, reactivity, activity, however, and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifest clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total dosage, to 200 to 300 mg/day), the average methemoglobin level was 8.2%. This was comparable to that observed in parallel patients who received placebo. Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with embryonic and fetal organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients with signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO2. Classically, methemoglobinemia is described as chocolate brown without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The recommended starting dose of isosorbide mononitrate extended-release tablets is 30 mg (given as a single 30 mg tablet) or as 15 mg of isosorbide mononitrate (given as a single tablet) once daily. After several days, the dosage may be increased to 120 mg (given as a single 120 mg tablet or as two 60 mg tablets) once daily. Rarely, 240 mg (given as two 120 mg tablets) may be required. In addition, the following spontaneous adverse event has been reported during the marketing of isosorbide mononitrate: syncope.

HOW SUPPLIED
Isosorbide Mononitrate Extended-Release Tablets 30 mg are off white, oval, scored tablets, debossed "3798" on one side and debossed "V" on the reverse side, packaged as follows: Bottles of 10, 100, 300 and 1000 tablets.

Isosorbide Mononitrate Extended-Release Tablets 60 mg are off white, capsule-shaped, scored tablets, debossed "3798" on one side and debossed "V" on the reverse side, packaged as follows: Bottles of 10, 100, 500 and 1000 tablets.

Isosorbide Mononitrate Extended-Release Tablets 120 mg are off white, oval, scored tablets, debossed "3798" on one side and debossed "V" on the reverse side, packaged as follows: Bottles of 10, 100, 300 and 1000 tablets.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).

Dispense in tight, light-resistant containers as described in USP.