NDA 19-091/S-008 JUN 13 2000

A.H. Robins Company
c/o Wyeth-Ayerst Research
Attention: Ms. Mary Alice Dankulich
170 North Radnor-Chester Road
St. Davids, PA 19087-5221

Dear Ms. Dankulich:

Please refer to your August 11, 1999 supplemental new drag application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ismo (isosorbide mononitrate) Tablets.

We acknowledge receipt of your submission dated May 11, 2000. Your submission of May 11, 2000 constituted a complete response to our September 29, 1999 approvable letter.

This supplemental new drug application provides for final printed labeling revised to read as follows:

A Geriatric Use subsection was added to the PRECAUTIONS section:

Geriatric Use

Clinical studies of Ismo did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, although age, renal, hepatic or cardiac dysfunction do not appear to have a clinically significant effect on the clearance of Ismo.

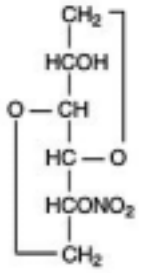
We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submission dated May 11, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR314.80and314.81.

Ismo
(isosorbide mononitrate)
20 mg tablets

DESCRIPTION

Isosorbide mononitrate is 1,4:3,6-dianhydro-D-glucitol,5-nitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 191.14. The organic nitrates are vasodilators, active on both arteries and veins. Each Ismo® tablet contains 20 mg of isosorbide mononitrate. The inactive ingredients in each tablet are D&C Yellow 10 Aluminum Lake, FD&C Yellow 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 20, povidone, silicon dioxide, sodium starch glycolate, titanium dioxide and hydroxypropyl cellulose.

CLINICAL PHARMACOLOGY

Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate (ISDN), and most of the clinical activity of the dinitrate is attributable to the mononitrate.
The principal pharmacological action of isosorbide mononitrate, due to its nitric oxide metabolite, is direct relaxation of vascular smooth muscle. The result is dilatation of peripheral arteries and veins, especially the latter. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Pharmacodynamics

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.
The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate has not been completely defined. In the only regimen of twice-daily isosorbide mononitrate that has been shown to avoid development of tolerance, the two doses of Ismo tablets are given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. The incidence and magnitude of such phenomena have appeared, in studies of other nitrates, to be highly dependent upon the schedule of nitrate administration.

Pharmacokinetics

In humans, isosorbide mononitrate is not subject to first pass metabolism in the liver. The absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. Maximum serum concentrations of isosorbide mononitrate are achieved 30 to 60 minutes after ingestion of Ismo.
The volume of distribution of isosorbide mononitrate is approximately 0.6 L/kg, and less than 4% is bound to plasma proteins. It is cleared from the serum by denitration to isosorbide; glucuronidation to the mononitrate glucuronide; and denitration/hydration to sorbitol. None of these metabolites is vasoactive. Less than 1% of administered isosorbide mononitrate is eliminated in the urine.
The overall elimination half-life of isosorbide mononitrate is about 5 hours; the rate of clearance is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly. In a single-dose study, the pharmacokinetics of isosorbide mononitrate were dose-proportional up to at least 60 mg.

Clinical Trials

Controlled trials of single doses of Ismo tablets have demonstrated that antianginal activity is present about 1 hour after dosing, with peak effect seen from 1 to 4 hours after dosing.
In placebo-controlled trials lasting 2 to 3 weeks, Ismo tablets were administered twice daily, in asymmetric regimens (with interdosing intervals of 7 and 17 hours) designed to avoid tolerance. One trial tested doses of 10 mg and 20 mg; one trial tested doses of 20 mg, 40 mg, and 60 mg; and three trials tested only doses of 20 mg. In each trial, the subjects were persons with known chronic stable angina, and the primary measure of efficacy was exercise tolerance on a standardized treadmill test. After initial dosing and for at least 3 weeks, exercise tolerance in patients treated with Ismo 20 mg tablets was significantly greater than that seen in patients treated with placebo, although there was some attenuation of effect with time. Treatment with Ismo tablets was superior to placebo for at least 12 hours after the first dose (i.e., 5 hours after the second dose) of each day. Significant tolerance and rebound phenomena were not observed.
The 10-mg dose was not unequivocally superior to placebo, while the effect of the 40-mg dose was similar to that of the 20-mg dose. The 60-mg dose appeared to be less effective, and it was associated with a rebound phenomenon (early-morning worsening).

INDICATIONS AND USAGE

Ismo tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of oral isosorbide mononitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide mononitrate is contraindicated in patients who are allergic to it.

WARNINGS

Amplification of the vasodilatory effects of Ismo by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.
The benefits of isosorbide mononitrate in patients with acute myocardial infarction or congestive heart failure have not been established. Because the effects of isosorbide mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings.

If isosorbide mononitrate is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

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 antianginal efficacy of Ismo tablets can be maintained by carefully following the prescribed schedule of dosing (two doses taken 7 hours apart). For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later.

As with other nitrates, daily headaches sometimes accompany treatment with isosorbide mononitrate. In 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 headache may be associated with simultaneous loss of antianginal efficacy. Aspirin and/or acetaminophen, on the other hand, often successfully relieve isosorbide mononitrate-induced headaches with no deleterious effect on isosorbide mononitrate's antianginal efficacy.

Treatment with isosorbide mononitrate may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effects were observed in mice exposed to oral isosorbide mononitrate for 104 weeks at doses of up to 900 mg/kg/day (102 × the human exposure comparing body surface area). Rats treated with 900 mg/kg/day for 26 weeks (225 × the human exposure comparing body surface area) and 500 mg/kg/day for the remaining 95 to 111 weeks (males and females, respectively) showed no evidence of tumors.

No mutagenic activity was seen in a variety of *in vitro* and *in vivo* assays.

No adverse effects on fertility were observed when isosorbide mononitrate was administered to male and female rats at doses up to 500 mg/kg/day (125 × the human exposure comparing body surface area).

Pregnancy Category C

Isosorbide mononitrate has been shown to be associated with stillbirths and neonatal death in rats receiving 500 mg/kg/day of isosorbide mononitrate (125 × the human exposure comparing body surface area). At 250 mg/kg/day, no adverse effects on reproduction and development were reported.

In rats and rabbits receiving isosorbide mononitrate at up to 250 mg/kg/day, no developmental abnormalities, fetal abnormalities, or other effects upon reproductive performance were detected; these doses are larger than the

maximum recommended human dose by factors between 70 (body-surface-area basis in rabbits) and 310 (body-weight basis, either species). In rats receiving 500 mg/kg/day, there were small but statistically significant increases in the rates of prolonged gestation, prolonged parturition, stillbirth, and neonatal death; and there were small but statistically significant decreases in birth weight, live litter size, and pup survival.
There are no adequate and well-controlled studies in pregnant women. Isosorbide mononitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether isosorbide mononitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide mononitrate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of isosorbide mononitrate in pediatric patients have not been established.

Geriatric Use

Clinical studies if Ismo® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, although age, renal, hepatic or cardiac dysfunction do not appear to have a clinically significant effect on the clearance of Ismo®.

ADVERSE REACTIONS

The table below shows the frequencies of the adverse reactions observed in more than 1% of the subjects (a) in 6 placebo-controlled domestic studies in which patients in the active-treatment arm received 20 mg of isosorbide mononitrate twice daily, and (b) in all studies in which patients received isosorbide mononitrate in a variety of regimens. In parentheses, the same table shows the frequencies with which these adverse reactions led to discontinuation of treatment. Overall, 11% of the patients who received isosorbide mononitrate in the six controlled U.S. studies discontinued treatment because of adverse reactions. Most of these discontinued because of headache. "Dizziness" and nausea were also frequently associated with withdrawal from these studies.

Frequency of Adverse Reactions (Discontinuations) *						
	6 Controlled Studies				92 Clinical Studies	
Dose	Placebo		20 mg		(varied)	
Patients	204		219		3344	
Headache	9%	(0%)	38%	(9%)	19%	(4.3%)
Dizziness	1%	(0%)	5%	(1%)	3%	(0.2%)
Nausea, Vomiting	<1%	(0%)	4%	(3%)	2%	(0.2%)

* Some individuals discontinued for multiple reasons.

Other adverse reactions, each reported by fewer than 1% of exposed patients, and in many cases of uncertain relation to drug treatment, were:
Cardiovascular: angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope.
Dermatologic: pruritus, rash.
Gastrointestinal: abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting.
Genitourinary: dysuria, impotence, urinary frequency.
Miscellaneous: asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors.
Musculoskeletal: arthralgia.
Neurologic: agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares.
Respiratory: bronchitis, pneumonia, upper-respiratory tract infection.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment see under **OVERDOSAGE.**

OVERDOSAGE

Hemodynamic Effects

The ill effects of isosorbide mononitrate overdose are generally the results of isosorbide mononitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Laboratory determinations of serum levels of isosorbide mononitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide mononitrate overdose.

There are no data suggesting what dose of isosorbide mononitrate is likely to be life-threatening in humans. In rats and mice, there is significant lethality at doses of 2000 mg/kg and 3000 mg/kg, respectively.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide mononitrate. In particular, dialysis is known to be ineffective in removing isosorbide mononitrate from the body.

No specific antagonist to the vasodilator effects of isosorbide mononitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide mononitrate overdose. Because the hypotension associated with isosorbide mononitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

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.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur 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_5 reductase 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 manifests 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 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8 to 11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; 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 moderate overdoses of 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 who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2.

Classically, methemoglobinemic blood 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 regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. Dosage adjustments are not necessary for elderly patients or patients with altered renal or hepatic function.

As noted above (**CLINICAL PHARMACOLOGY**), multiple studies of organic nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. The dosing regimen for Ismo tablets provides a daily nitrate-free interval to avoid the development of this tolerance.

As also noted under **CLINICAL PHARMACOLOGY,** well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice-daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than about 12 hours of continuous antianginal efficacy per day.

In clinical trials, Ismo tablets have been administered in a variety of regimens. Single doses less than 20 mg have not been adequately studied, while single doses greater than 20 mg have demonstrated no greater efficacy than doses of 20 mg.

HOW SUPPLIED

Ismo® (isosorbide mononitrate) tablets, 20 mg, are available in bottles of 100 (NDC 0008-0771-01) and in unit dose packages of 10 blister strips of 10 tablets (NDC 0008-0771-02). Each orange, round, film-coated tablet is engraved "ISMO 20" on one side and scored on the reverse side.

Store at controlled room temperature between 20°C and 25°C (68°F and 77°F).

Dispense in tight container.

Manufactured by:
Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
Distributed jointly with:
Boehringer Mannheim Pharmaceuticals Corp.
Rockville, MD 20850

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