Approved Date: June 13th, 2007
Revision Date: January 15th, 2018

Package Insert of Isosorbide Mononitrate Sustained-release Capsules (II)

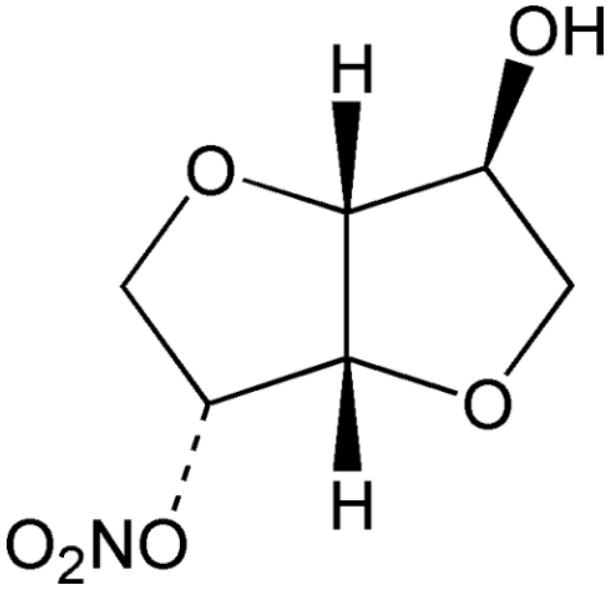
Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]

Generic Name: Isosorbide Mononitrate Sustained-release Capsules (II)
Chinese Pinyin: Danxiaosuan Yishanlizhi Huanshi Jiaonang (II)

[Active Ingredients]

The active pharmaceutical ingredient (API) of this product is isosorbide mononitrate (ISMN), an organic nitrate and the major biologically active metabolite of isosorbide dinitrate (ISDN), is a vasodilator with effects on both arteries and veins.
Chemical Name of the API: 1,4:3,6- dianhydro-,D-glucitol 5-nitrate.
Structural Formula:



Molecular Formula: $C_6H_9NO_6$
Molecular Weight: 191.14

[Inactive Ingredient]

Sucrose, Corn starch, Cellulose microcrystalline, Hypromellose, Pharmaceutical Grade Sucrose pellet, Hydroxypropyl Methylcellulose, Silicon dioxide, Hexadecan-1-ol, Ethylcellulose, Acrylic resin, Castor oil, Talc Powder, Ethanol.

[Properties]

This product is a hard capsule, containing white or off-white pellets.

[Indications]

Isosorbide Mononitrate Extended-Release Capsules 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.

[Strength]

40 mg

[Dosage and Administration]
The recommended starting dose of Isosorbide Mononitrate Extended-Release Capsules is 40 mg once daily. The daily dose of Isosorbide Mononitrate Extended-Release Capsules should be taken in the morning on arising. Isosorbide Mononitrate Extended-Release Capsules should not be chewed or crushed and should be swallowed together with a half-glassful of fluid.

[Adverse Reactions]

The table below shows the frequencies of the adverse events that occurred in >5% of the subjects in three placebo-controlled North American studies, in which patients in the active treatment arm received 30 mg, 60 mg, 120 mg, or 240 mg of Isosorbide Mononitrate Extended-Release Tablets once daily. In parentheses, the same table shows the frequencies with which these adverse events were associated with the discontinuation of treatment. Overall, 8% of the patients who received 30 mg, 60 mg, 120 mg, or 240 mg of isosorbide mononitrate in the three placebo-controlled North American studies discontinued treatment because of adverse events. Most of these discontinued because of headache. Dizziness was rarely associated with withdrawal from these studies. Since headache appears to be a dose-related adverse effect and tends to disappear with continued treatment, it is recommended that ISMN treatment be initiated at low doses for several days before being increased to desired levels.

FREQUENCY AND ADVERSE EVENTS (DISCONTINUED)[a]

Three Controlled North American Studies					
Dose	Placebo	30 mg	60 mg	120 mg*	240 mg*
Patients	96	60	102	65	65
Headache	15% (0%)	38% (5%)	51% (8%)	42% (5%)	57% (8%)
Dizziness	4% (0%)	8% (0%)	11% (1%)	9% (2%)	9% (2%)

* Patients were started on 60 mg and titrated to their final dose.

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 only 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:

Autonomic Nervous System Disorders: Dry mouth, hot flushes.

Body as a Whole: Asthenia, back pain, chest pain, edema, fatigue, fever, flu-like symptoms, malaise, rigors.

Cardiovascular Disorders, General: Cardiac failure, hypertension, hypotension.

Central and Peripheral Nervous System Disorders: Dizziness, headache, hypoesthesia, migraine, neuritis, paresis, paresthesia, ptosis, tremor, vertigo.
Gastrointestinal System Disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastric ulcer, gastritis, glossitis, hemorrhagic gastric ulcer, hemorrhoids, loose stools, melena, nausea, vomiting.

Hearing and Vestibular Disorders: Earache, tinnitus, tympanic membrane perforation.

Heart Rate and Rhythm Disorders: Arrhythmia, arrhythmia atrial, atrial fibrillation, bradycardia, bundle branch block, extrasystole, palpitation, tachycardia, ventricular tachycardia.

Liver and Biliary System Disorders: SGOT increase, SGPT increase.

Metabolic and Nutritional Disorders: Hyperuricemia, hypokalemia.

Musculoskeletal System Disorders: Arthralgia, frozen shoulder, muscle weakness, musculoskeletal pain, myalgia, myositis, tendon disorder, torticollis.

Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris aggravated, heart murmur, heart sound abnormal, myocardial infarction, Q wave abnormality.

Platelet, Bleeding and Clotting Disorders: Purpura, thrombocytopenia.

Psychiatric Disorders: Anxiety, concentration impaired, confusion, decreased libido, depression, impotence, insomnia, nervousness, paroniria, somnolence.

Red Blood Cell Disorder: Hypochromic anemia.

Reproductive Disorders, Female: Atrophic vaginitis, breast pain.

Resistance Mechanism Disorders: Bacterial infection, moniliasis, viral infection.

Respiratory System Disorders: Bronchitis, bronchospasm, coughing, dyspnea, increased sputum, nasal congestion, pharyngitis, pneumonia, pulmonary infiltration, rales, rhinitis, sinusitis.

Skin and Appendages Disorders: Acne, hair texture abnormal, increased sweating, pruritus, rash, skin nodule.

Urinary System Disorders: Polyuria, renal calculus, urinary tract infection.

Vascular (Extracardiac) Disorders: Flushing, intermittent claudication, leg ulcer, varicose vein.

Vision Disorders: Conjunctivitis, photophobia, vision abnormal. In addition, the following spontaneous adverse event has been reported during the marketing of isosorbide mononitrate: syncope.

[Contraindications]
Isosorbide Mononitrate Extended-Release Tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

[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 Isosorbide Mononitrate Extended-Release Capsules can be maintained by carefully following the prescribed schedule of dosing. For most patients, this can be accomplished by taking the dose on arising.

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 or acetaminophen often successfully relieves 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.

[Use in Pregnant and Lactation]

Teratogenic effects Pregnancy Category B

In studies designed to detect effects of isosorbide mononitrate on embryo-fetal development, doses of up to 240 or 248 mg/kg/day, administered to pregnant rats and rabbits, were unassociated with evidence of such effects. These animal doses are about 100 times the maximum recommended human dose (120 mg in a 50 kg woman) when comparison is based on body weight; when comparison is based on body surface area, the rat dose is about 17 times the human dose and the rabbit dose is about 38 times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Isosorbide Mononitrate Extended-Release Capsules should be used during pregnancy only if clearly needed.

Nonteratogenic effects

Neonatal survival and development and incidence of stillbirths were adversely affected when pregnant rats were administered oral doses of 750 (but not 300) mg isosorbide mononitrate/kg/day during late gestation and lactation. This dose (about 312 times the human dose when comparison is based on body weight and 54 times the human dose when comparison is based on body surface area) was associated with decreases in maternal weight gain and motor activity and evidence of impaired lactation.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ISMN is administered to a nursing mother.

[Pediatric Use]

The safety and effectiveness of ISMN in pediatric patients have not been established.

[Geriatric Use]

Clinical studies of isosorbide mononitrate extended-release tablets did not include sufficient information on patients age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience for isosorbide mononitrate extended-release tablets has not identified differences in response between elderly and younger patients. Clinical experience for organic nitrates reported in the literature identified a potential for severe hypotension and increased sensitivity to nitrates in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Elderly patients may have reduced baroreceptor function and may develop severe orthostatic hypotension when vasodilators are used. Isosorbide Mononitrate Extended-Release Capsules should therefore be used with caution in elderly patients who may be volume depleted, on multiple medications or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.
Elderly patients may be more susceptible to hypotension and may be at a greater risk of falling at therapeutic doses of nitroglycerin.
Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy, particularly in the elderly.

[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.

[Pharmacology and Toxicology]

Clinical Pharmacology

Mechanism of Action

The Isosorbide Mononitrate Extended-Release Capsules is an oral extended-release formulation of ISMN, the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is attributable to the mononitrate.

The principal pharmacological action of ISMN and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood, 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.

[Pharmacokinetics]

After oral administration of ISMN as a solution or immediate-release tablets, maximum plasma concentrations of ISMN are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. After intravenous administration, ISMN is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6-0.7 L/kg. Isosorbide mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Isosorbide mononitrate is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. Isosorbide mononitrate is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least six different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least five metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half-life of ISMN is approximately 5 hours.

The disposition of ISMN in patients with various degrees of renal insufficiency, liver cirrhosis, or cardiac dysfunction was evaluated and found to be similar to that observed in healthy subjects. The elimination half-life of ISMN was not prolonged, and there was no drug accumulation in patients with chronic renal failure after multiple oral dosing.

The pharmacokinetics and/or bioavailability of Isosorbide Mononitrate Extended-Release Tablets have been studied in both normal volunteers and patients following single- and multiple-dose administration. Data from these studies suggest that the pharmacokinetics of ISMN admin-istered as Isosorbide Mononitrate Extended-Release Tablets are similar between normal healthy volunteers and patients with angina pectoris. In single- and multiple-dose studies, the pharmacokinetics of ISMN were dose proportional between 30 mg and 240 mg.

In a multiple dose study, the effect of age on the pharmacokinetic profile of Isosorbide Mononitrate Extended Release Tablets 60 mg and 120 mg (2 x 60 mg) was evaluated in subjects ⩾45 years. The results of that study indicate that there are no significant differences in any of the pharmacokinetic variables of ISMN between elderly (⩾65 years) and younger individuals (45-64 years) for the isosorbide mononitrate extended-release 60 mg dose. The administration of isosorbide mono-nitrate extended-release 120 mg (2 x 60 mg tablets every 24 hours for 7 days) produced a dose-proportional increase in C_{max} and AUC, without changes in T_{max} or the terminal half-life. The older group (65-74 years) showed 30% lower apparent oral clearance (Cl/F) following the higher dose, i.e., 120 mg, compared to the younger group (45-64 years); Cl/F was not different between the two groups following the 60 mg regimen. While Cl/F was independent of dose in the younger group, the older group showed slightly lower Cl/F following the 120 mg regimen compared to the 60 mg regimen. Differences between the two age groups, however, were not statistically significant. In the same study, females showed a slight (15%) reduction in clearance when the dose was increased. Females showed higher AUCs and C_{max} compared to males, but these differences were accounted for by differences in body weight between the two groups. When the data were analyzed using age as a variable, the results indicated that there were no significant differences in any of the pharmacokinetic variables of ISMN between older (⩾65 years) and younger individuals (45-64 years). The results of this study, however, should be viewed with 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 Capsules.

	SINGLE-DOSE STUDIES		MULTIPLE-DOSE STUDIES	
PARAMETER	ISMN 60 mg	ISMN Extended-Release Tablets 60 mg	ISMN Extended-Release Tablets 60 mg	ISMN Extended-Release Tablets 120 mg
C_{max}(ng/mL)	1242-1534	424-541	557-572	1151-1180
T_{max}(hr)	0.6-0.7	3.1-4.5	2.9-4.2	3.1-3.2
AUC (ng•hr/mL)	8189-8313	5990-7452	6625-7555	14241-16800
$T_{½}$ (hr)	4.8-5.1	6.3-6.6	6.2-6.3	6.2-6.4
Cl/F (mL/min)	120-122	151-187	132-151	119-140

Food Effects
The influence of food on the bioavailability of ISMN after single-dose administration of Isosorbide Mononitrate Extended- Release Tablets 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 T_{max}) but not the extent (AUC) of absorption of ISMN.

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 10 tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 10 tablets/plate, two plates/carton

Aluminum-plastic blister packaging, 10 tablets/plate, three plates/carton

[Shelf-Life]
24 months

[Executive Standard]
National Medical Products Agency Standard WS_1-(X-041)-2005Z

[Approval Number]
Guo Yao Zhun Zi H19991018

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