ISOSORBIDE-5-MONONITRATE

Montra®

30 mg and 60 mg Sustained Release Capsule

Anti-angina

FORMULATION
Each sustained release capsule contains:
Isosorbide-5-mononitrate…….. 30 mg or 60 mg

PRODUCT DESCRIPTIONS
Montra® 30mg Sustained Release Capsule: White to off-white spherical to oval pellets encapsulated in hard gelatin, size "3" capsule with grey opaque cap and clear transparent body
Montra® 60mg Sustained Release Capsule: White to off-white spherical to oval pellets encapsulated in hard gelatin, size "3" capsule with blue opaque cap and clear transparent body

PHARMACODYNAMICS
Isosorbide-5-mononitrate (ISMN), an active metabolite of isosorbide dinitrate, acts by relaxing vascular smooth muscles producing vasodilatation of both arteries and veins, with the latter effect predominating. The effect of treatment is dependent on the dose. Low plasma concentrations lead to venous dilatation, resulting in peripheral pooling of blood, decreased venous return and reduction in left ventricular end-diastolic pressure (preload). High plasma concentrations also dilate the arteries reducing systemic vascular resistance and arterial pressure leading to a reduction in cardiac afterload. Dilatation of coronary arteries also occurs. By decreasing end diastolic pressure and volume, ISMN decreases intramural pressure resulting in improvement in subendocardial blood flow. Thus, after administering ISMN, there is reduced cardiac workload and improved oxygen supply/ demand balance in the myocardium.

PHARMACOKINETICS
ISMN in sustained-release formulation is gradually released over a 10-hour period, independent of pH, according to a first order process. This prolonged absorption phase results in reduced and delayed peak plasma levels compared to conventional tablets of ISMN. Peak plasma levels of about 3000 nmol/L were reported to be obtained within approximately 4 hours after administration of 60 mg ISMN sustained-release tablets. Plasma concentrations gradually decrease to 500 nmol/L 24 hours after dose intake. Bioavailability of ISMN in oral sustained-release formulation is about 90% compared to conventional immediate release tablets. Food does not significantly affect ISMN absorption.

The bioequivalence of ISMN, one x 120 mg capsule versus two x 60 mg tablets, was assessed in a randomized, two-treatment, two-period, two-way, crossover study. After a single oral dose of 120 mg capsule to healthy fasted adults, peak plasma concentration (C_{max}) of ISMN (804.249 ng/mL) was achieved within 2.917 hours (T_{max}). Values of C_{max}, T_{max} and area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) were comparable for the tablet and capsule and the two formats were bioequivalent.

ISMN's plasma protein binding is about 5%. The volume of distribution is about 0.6 L/kg and total clearance is around 115 mL/min. ISMN is metabolized primarily by the liver but it is not subject to first pass effect. About 50% of a dose of ISMN undergoes denitration to form isosorbide, followed by partial dehydration to form sorbitol. ISMN also undergoes glucuronidation to form 5-mononitrate glucuronide. About 96% of the administered dose is excreted in urine within 5 days and only about 1% is eliminated in the feces; most excretion (about 93%) occurs within 48 hours. 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. The mean plasma elimination half-life of ISMN is about 5 hours.

In patients with various degrees of renal insufficiency, liver cirrhosis or cardiac dysfunction, the disposition of ISMN was 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.

Impairment of the liver or kidney has no major influence on the pharmacokinetic properties of ISMN.

ISMN sustained release formats have been shown to be effective in monotherapy as well as in combination with chronic beta-blocker therapy. The clinical effects may be attenuated during repeated administration with nitrates in high doses and/or frequent administration. This can be avoided by allowing low plasma levels for a certain period of the dosage interval. The sustained release format of ISMN produces a plasma profile that provides high plasma levels during daytime and low night-time plasma levels when administered once daily in the morning.

INDICATIONS
- Prophylaxis of anginal attacks in patients with chronic stable angina pectoris associated with coronary artery disease

ISMN is NOT indicated for the management of acute attacks of angina pectoris

DOSAGE AND ADMINISTRATION
Initial Adult Dose: Orally, 30 mg once daily in the morning for the first 2 to 4 days.
- Dose can be increased to 60 mg or 120 mg taken once daily in the morning. Or, as prescribed by a physician
- Swallow capsule whole with a glass of water
- Can be taken with or without food

CONTRAINDICATIONS
- Hypersensitivity to isosorbide-5-mononitrate or to other nitrates/nitrites or any component in the formulation
- Acute circulatory failure associated with marked hypotension (shock and states of collapse)
- Angle-closure glaucoma
- Functional or organic gastrointestinal (GI) hypermotility or malabsorption syndrome
- Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage)
- Myocardial insufficiency due to obstruction (e.g., in the presence of aortic or mitral stenosis or of constrictive pericarditis)
- Obstructive hypertrophic cardiomyopathy
- Pericarditis
- Hypotension and/or cardiogenic shock
- Postural or orthostatic hypotension
- Severe anemia
- Concurrent therapy with phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil, tadalafil, vardenafil) since severe, potentially fatal hypotensive episodes can occur

WARNINGS AND PRECAUTIONS
The benefits and safety of ISMN in anginal patients with acute myocardial infarction or congestive heart failure have not been established. Since the effects of ISMN are difficult to terminate rapidly, this drug is not recommended in these settings.

Use with caution in patients who may be volume depleted or who are already hypotensive because severe hypotension, particularly with upright posture, may occur with even small doses of ISMN. Patients with systolic blood pressure less than 90 mmHg or greater than 30 mmHg below baseline generally should not receive nitrates. Hypotension induced by ISMN may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

There is risk of developing tolerance to the hemodynamic and antianginal effects if higher doses (>120 mg/day) and/or more frequent doses (e.g., twice daily) of ISMN are administered. Administer ISMN sustained-release capsules once daily to reduce risk of developing tolerance. (see **Dosage and Administration**)

Tolerance to the individual nitrates and nitrites and cross tolerance among these drugs may occur with repeated, prolonged use. Tolerance to the vascular and antianginal effects of the drugs has been shown in studies, by experience from occupational exposure, and in isolated *in vitro* tissue experiments; such tolerance is a principal factor limiting the efficacy of long-term nitrate therapy. Tolerance to nitrates appears to be associated with high and/or sustained plasma drug concentrations and frequent administrations. There is physical dependence in industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers.

Although no documented rebound phenomena were reported upon sudden withdrawal of sustained release ISMN, such abrupt withdrawal is not recommended because of the possibility of severe exacerbation of anginal symptoms.

Headaches or severe hypotension (e.g., weakness or dizziness, particularly when arising suddenly from a recumbent position) may occur.

Use with caution in patients with severe cerebral arteriosclerosis.

Use with caution in patients with arterial hypoxia due to anemia. Likewise, caution should be exercised in patients with hypoxemia and a ventilation/perfusion imbalance due to lung disease or ischemic heart failure. Patients with angina pectoris, myocardial infarction or cerebral ischemia frequently suffer from small airways abnormalities (i.e., alveolar hypoxia). In these situations, vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. ISMN, as a potent vasodilator, could reverse this protective vasoconstriction and thus result in increased perfusion to poorly ventilated areas, worsening of the ventilation/ perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

PDE-5 inhibitors are contraindicated in patients receiving nitrates/nitrites, given regularly or intermittently, since severe, potentially fatal hypotensive episodes may occur. However, the use of organic nitrates/nitrites in patients receiving PDE-5 inhibitors may not be completely avoidable, provided sufficient time has elapsed between the use of PDE-5 inhibitors and administration of nitrates/nitrites. Although it is not known how much time must elapse between the use of sildenafil and administration of nitrate/nitrite, pharmacokinetic data suggest that these latter agents should not be given within 24 hours of sildenafil administration since an exaggerated hypotensive response is likely; plasma sildenafil concentrations 24 hours after a dose are substantially lower than peak concentrations.

Exercise caution when engaging in activities requiring mental alertness, i.e., driving or operating machinery, since patients may experience faintness and/or dizziness.

INTERACTIONS WITH OTHER MEDICAMENTS
Concomitant administration with PDE-5 inhibitors can potentiate the vasodilatory effect of organic nitrates/nitrites resulting in life-threatening hypotension with syncope or myocardial infarction and death. Thus, PDE-5 inhibitors should not be given to patients on existing therapy with ISMN. (see **Warnings and Precautions**)

Dihydroergotamine may counteract the coronary vasodilatory effect of nitrates. Use concomitantly with caution since this may increase risk of angina precipitation.

Adding ISMN to propranolol treatment in patients with cirrhosis and portal hypertension led to a marked fall in portal pressure, a reduction in hepatic blood flow, cardiac output and mean arterial blood pressure.

Patients receiving other vasodilators, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, major tranquilizers, phenothiazines, and nitrates/nitrites should be observed for possible additive hypotensive effects. Dose adjustments of either the nitrate/nitrite or the other agent with hypotensive activity may be necessary to avoid orthostatic hypotension during concomitant use.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
• PREGNANCY AND LACTATION
Pregnancy Category C. There are no available studies in pregnant women. ISMN should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether ISMN is excreted in breastmilk. Exercise caution when administering the drug to breastfeeding women.

• CHILDREN
The safety and efficacy of ISMN in children have not been established.

UNDESIRABLE EFFECTS
Adverse reactions to nitrates mainly involve the central nervous system and cardiovascular system. Headache the most frequent adverse effect, may be severe (persistent or transient) and is perceived as a pulsating, throbbing sensation, frequently seen early in therapy, usually diminishes rapidly, and may disappear within several days to weeks of continuous therapy.

Postural hypotension may occur and may cause dizziness, weakness and other signs of cerebral ischemia. Transient flushing may also occur.

Other reported adverse events are as follows:
Body as a Whole: Asthenia, back pain, chest pain, edema, peripheral edema, fatigue, feeling of warmth, fever, flu-like symptoms, malaise, pain, rigors, syncope
Autonomic Nervous System: Dry mouth, hot flushes
Cardiovascular: Angina pectoris aggravated, abnormal heart sounds, arrhythmia, atrial arrhythmia, atrial fibrillation, AV block, bradycardia, bundle branch block, cardiac failure, circulatory failure, extrasystole, heart murmur, hypertension/rebound hypertension, hypotension/postural hypotension, myocardial infarction, palpitation, peripheral ischemia, tachycardia, reflex tachycardia, vasospasm, ventricular tachycardia, ECG abnormal, Q-wave abnormality, T-wave changes
Central and Peripheral Nervous System: Agitation, amnesia, anxiety, cerebrovascular disorder, confusion, decreased libido, impotence, depression, dizziness, headache/migraine, hypoesthesia, impaired concentration, insomnia, nervousness, neuritis, paresis, paresthesia, paroniria, somnolence, tremor, vertigo
Gastrointestinal: Abdominal pain, constipation, diarrhea, gastric ulcer/hemorrhagic gastric ulcer, duodenal ulcer, dyspepsia, eructation, flatulence, gastritis, glossitis, heartburn, hemorrhoids, intestinal obstruction, loose stools, melena, nausea, pharyngeal disorder, poor appetite, tooth disorder, vomiting
Hepatic and Biliary: Biliary pain, cholecystitis, hepatomegaly
Metabolic and Nutritional: Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, weight decrease, weight increase; Elevations in the following: gamma glutamyl transpeptidase (GT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), non-protein nitrogen
Musculoskeletal: Arthralgia, arthritis, arthropathy, arthrosis, frozen shoulder, muscle weakness, musculoskeletal pain, myalgia, myositis, tendon disorder, torticollis
Hematologic: Purpura, thrombocytopenia, anemia, hypochromic anemia, epistaxis, leukopenia, leukocytosis
Reproductive: Atrophic vaginitis, female breast pain, prostatic disorder
Respiratory: Bronchitis, bronchospasm, coughing, dyspnea, increased sputum, nasal congestion, pharyngitis, pneumonia, pulmonary infiltration, rales, respiratory disorder, respiratory infection, rhinitis, sinusitis
Skin and Appendages: Allergy/allergic reaction, acne, abnormal hair texture, eczema, increased sweating, cold sweat, pruritus, rash, rash erythematous, rash psoriaform, skin disorder, skin nodule, pallor
Urinary: Albuminuria, hematuria, glycosuria, polyuria, renal calculus, urinary bladder diverticulum, urinary tract infection
Vascular (Extracardiac): Flushing, intermittent claudication, leg ulcer, varicose vein
Ophthalmologic: Abnormal vision/blurred vision, amaurosis fugax, conjunctivitis, diplopia, photophobia, ptosis
Hearing and Vestibular: Earache, tinnitus, tympanic membrane perforation
Others: Infection (bacterial, viral), moniliasis

OVERDOSE AND TREATMENT
The common symptoms of nitrate overdose includes severe hypotension, tachycardia, bradycardia, heart block, palpitation, death secondary to circulatory collapse, vertigo, confusion, fever, syncope (particularly in the upright posture), persistent throbbing headache, visual disturbances, increased intracranial pressure, paralysis, and coma followed by seizures, flushing and diaphoresis, cold and clammy skin, nausea and vomiting, colic and bloody diarrhea, dyspnea, and methemoglobinemia.

Manage nitrate overdose by inducing emesis, then administer activated charcoal. In the occurrence of marked hypotension, place the patient in supine position with legs elevated. Give further symptomatic treatment, including intravenous fluids, if necessary. If bradycardia is present, atropine may be useful. When methemoglobinemia is diagnosed, intravenous administration of methylene blue 1 to 2 mg/kg may be required. Management of ISMN overdosage in patients with renal disease or congestive heart failure may be difficult, and may require invasive monitoring.

Dialysis is ineffective in removing ISMN from the body.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, report to the FDA: at www.fda.gov.ph and Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP OUT OF SIGHT AND REACH OF CHILDREN

AVAILABILITY:
Isosorbide-5-mononitrate (Montra®) 30 mg Sustained Release Capsule in blister pack x 10's (box of 100's)
Isosorbide-5-mononitrate (Montra®) 60 mg Sustained Release Capsule in blister pack x 10's (box of 100's)

DATE OF REVISION: September 2009

THE153062IN01
Reg. IPOPHIL

Manufactured by **Inventia Healthcare Pvt. Ltd.**
F1-F1/1, Additional Ambernath M.I.D.C
Ambernath (East) 421 506, Dist. Thane, India
Imported & Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

AC2045L04