PRODUCT MONOGRAPH

[Pr]Dom-ISMN

(isosorbide-5-mononitrate)

60 mg extended release tablets

Antianginal Agent

DOMINION PHARMACAL .
6111 Royalmount Ave., Suite 100
Montreal, Quebec
H4P 2T4

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PRODUCT MONOGRAPH

NAME OF DRUG

Dom-ISMN

(isosorbide-5-mononitrate)

60 mg extended release tablets

THERAPEUTIC CLASSIFICATION

Antianginal agent

ACTIONS AND CLINICAL PHARMACOLOGY

As with other organic nitrates, the principal pharmacological action of isosorbide-5-mononitrate, the major active metabolite of isosorbide dinitrate (ISDN), is relaxation of vascular smooth muscle and consequent dilation 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 (pre-load). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (after-load). Dilation of the coronary arteries also occurs. The hemodynamic responses to isosorbide-5-mononitrate are similar to those produced by other nitrates.

Pharmacodynamics

Dosage 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. Prolonged administration of nitrate drugs according to traditionally recommended dosage regimens has been shown to produce tolerance. Tolerance results in a loss of efficacy. 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, nitrate effectiveness was 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. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. The drug-free interval sufficient to avoid tolerance to isosorbide-5-mononitrate has not been completely defined. Isosorbide-5-mononitrate tablets during long-term use over 42 days dosed at 120 mg once daily continued to improve exercise performance at 4 hours and 12 hours after dosing but its effects (although better than placebo) are less than or at best equal to the effects of the first dose of 60 mg.

Considering the pharmacokinetic profile of isosorbide-5-mononitrate and its long half-life (see Pharmacokinetics), clinical efficacy is consistent with that observed for other organic nitrates.

Pharmacokinetics

After oral administration of isosorbide-5-mononitrate as a solution or immediate-release tablets, maximum plasma concentrations of isosorbide-5-mononitrate are achieved in 30 to 60 minutes with an absolute bioavailability of approximately 100%. After intravenous administration, isosorbide-5-mononitrate is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6 - 0.7 L/kg. Isosorbide-5-mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Isosorbide-5-mononitrate is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. Isosorbide-5-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 isosorbide-5-mononitrate is approximately 5 hours.

The disposition of isosorbide-5-mononitrate 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 isosorbide-5-mononitrate was not prolonged, and there was no drug accumulation in patients with chronic renal failure after multiple oral dosing.

Impaired liver or kidney function has no major influence on the pharmacokinetic properties.

Food intake may decrease the rate (increase in T_{max}) but not the extent (AUC) of absorption of isosorbide-5-mononitrate.

With the extended release formulation of Dom-ISMN, isosorbide-5-mononitrate is gradually released, independent of pH, over a 10-hour period, according to a first order process.

This prolongation of the absorption phase results in reduced and delayed peak plasma levels compared to conventional tablets of isosorbide-5-mononitrate. After administration of 60 mg of isosorbide-5-mononitrate extended release tablets, peak plasma levels of around 3000 nmol/L are usually obtained within approximately 4 hours. The plasma concentrations then gradually fall to around 500 nmol/L at the end of the dosage interval (24 hours after dose intake).

INDICATIONS AND CLINICAL USE

Dom-ISMN (isosorbide-5-mononitrate) is indicated for the prevention of anginal attacks in patients with chronic stable angina pectoris associated with coronary artery disease. Dom-ISMN is not intended for the immediate relief of acute attacks of angina pectoris.

CONTRAINDICATIONS

- Known hypersensitivity to isosorbide-5-mononitrate or to other nitrates or nitrites.
- Acute circulatory failure associated with marked hypotension (shock and states of collapse).
- Postural hypotension
- Myocardial insufficiency due to obstruction (e.g., in the presence of aortic or mitral stenosis or of constrictive pericarditis).
- Increased intracranial pressure.
- Severe anemia.
- Concomitant use of nitrates, either regularly and/or intermittently, with phosphodiesterase type 5 Inhibitors (e.g. sildenafil, tadalafil, vardenafil) is absolutely contraindicated.

WARNINGS

The benefits and safety of isosorbide-5-mononitrate in anginal patients with acute myocardial infarction or congestive heart failure have not been established. Because the effects of isosorbide-5-mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings.

Abrupt withdrawal may occasionally aggravate anginal symptoms. To avoid possible withdrawal effects, the administration of isosorbide-5-mononitrate should be gradually reduced and not abruptly discontinued.

Caution should be observed in patients with severe cerebral arteriosclerosis or severe hypotension.

PRECAUTIONS

Headaches or symptoms of severe hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur.

Caution should be exercised when using nitrates in patients prone to, or who might be affected by, hypotension. Isosorbide-5-mononitrate should therefore be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood

pressure (e.g., below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension.

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. There is, moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine, clinical use of oral isosorbide-5-mononitrate has not been fully elucidated. Caution should be exercised in patients with arterial hypoxemia due to anemia (see CONTRAINDICATIONS). Similarly, caution is called for 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 abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, isosorbide-5-mononitrate 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.

Tolerance to isosorbide-5-mononitrate with cross tolerance to other nitrates or nitrites may occur (see ACTIONS AND CLINICAL PHARMACOLOGY). As tolerance to isosorbide-5-mononitrate develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

Use in Pregnancy

Teratogenic Effects: In studies designed to detect effects of isosorbide-5-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. No adverse effects on reproduction or fetal development were reported. These animal doses are about 100 times the maximum recommended human dose 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 no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, isosorbide-5-mononitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic 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-5-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.

Use in Nursing Mothers

It is not known whether isosorbide-5-mononitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide-5-mononitrate is administered to a nursing mother.

Use in Children

The safety and efficacy of isosorbide-5-mononitrate in children have not been established. Therefore, its use is not recommended.

Drug Interactions

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of isosorbide-5-mononitrate.

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.

Concomitant use of isosorbide-5-mononitrate and phosphodiesterase type 5 Inhibitors (e.g. sildenafil, tadalafil, vardenafil) can potentiate the hypotensive effect of isosorbide-5-mononitrate. This could result in life-threatening hypotension with syncope or myocardial infarction and death. Therefore, phosphodiesterase type 5 Inhibitors (e.g. sildenafil, tadalafil, vardenafil) should not be given to patients receiving isosorbide-5-mononitrate therapy.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

ADVERSE REACTIONS

In 17 clinical trials, both controlled and uncontrolled, 861 patients were treated with isosorbide-5-mononitrate 30 mg to 240 mg once daily, alone or in combination with b-adrenergic blocking agents. Adverse events were reported in 71% of the patients.
Discontinuation of therapy due to adverse reactions was required in 8% of the patients. Most of these were discontinued because of headache. Dizziness, myocardial infarction, nausea, and vertigo were also associated with withdrawal from these studies. The most common adverse events were headache, dizziness, fatigue, nausea and flushing.

The following adverse events were reported by >1-3% of patients: myocardial infarction, postural hypotension, tachycardia, angina pectoris, somnolence, coughing, paresthesia, vertigo, abdominal pain, diarrhea, flatulence, extra systoles, palpitation, aggravated angina, insomnia, dyspnea, respiratory infection, increased sweating, vasospasm, abnormal vision, back pain, musculoskeletal pain, dyspepsia, chest pain, rhinitis, constipation.

The following adverse events were reported in ≤ 1% of the patients:

Cardiovascular: bundle branch block, cardiac failure, circulatory failure, hypotension, hypertension, syncope, arrhythmia, AV block, bradycardia, atrial fibrillation, heart murmur, abnormal heart sound, Q-wave abnormality, T-wave changes, ECG abnormal.

Dermatological: rash, pruritus, eczema, acne, rash erythematous, rash psoriaform, abnormal hair texture, skin disorder.

Gastrointestinal: duodenal ulcer, eructation, hemorrhagic gastric ulcer, gastritis, hemorrhoids, intestinal obstruction, melena, dry mouth, pharynx disorder, tooth disorder, vomiting, loose stools, glossitis.

Genitourinary: atrophic vaginitis, prostatic disorder, renal calculus, urinary bladder diverticulum, urinary tract infection, polyuria.

Miscellaneous: allergic reaction, asthenia, female breast pain, edema, feeling of warmth, fever, flu-like symptoms, malaise, rigors, earache, biliary pain, cholecystitis, hepatomegaly, diabetes mellitus, gout, weight decrease, weight increase, peripheral edema, tinnitus, epistaxis, purpura, infection, bacterial infection, cerebrovascular disorder, intermittent claudication, leg ulcer, peripheral ischemia, varicose vein, amaurosis fugax, conjunctivitis, diplopia, photophobia, moniliasis, skin nodule, tympanic membrane perforation, allergy, pain.

Musculoskeletal: arthralgia, arthritis, arthropathy, arthrosis, frozen shoulder, muscle weakness, myalgia, myositis, torticollis, tendon disorder.

Neurological: hypoesthesia, migraine, neuritis, tremor, agitation, amnesia, impaired concentration, depression, decreased libido, nervousness, paroniria, confusion, anxiety, paresis, ptosis, impotence.

Respiratory: bronchitis, bronchospasm, pharyngitis, pneumonia, rales, respiratory disorder, pulmonary infiltration, increased sputum, sinusitis, nasal congestion.

Laboratory Changes: albuminuria, hematuria, gamma GT increased, SGOT increased, SGPT increased, hypercholesterolemia, hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, increased non-protein nitrogen, thrombocytopenia, anemia, leukopenia, leukocytosis, glycosuria.

REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Hemodynamic Effects

Symptoms of isosorbide-5-mononitrate overdose are generally the results of vasodilation, 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.

No specific antagonist to the vasodilator effects of isosorbide-5-mononitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide-5-mononitrate overdose. Because the hypotension associated with isosorbide-5-mononitrate overdose is the result of venodilation 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.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide-5-mononitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

The use of epinephrine or other vasoconstrictors is ineffective in reversing the severe hypotensive effects of overdose and is therefore contraindicated in this situation.

Dialysis is known to be ineffective in removing isosorbide-5-mononitrate from the body.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it may occur as a side effect of isosorbide-5-mononitrate. Nitrate ions liberated during metabolism of isosorbide-5-mononitrate can oxidize hemoglobin into methemoglobin. In patients totally without cytochrome b5 reductase activity, about 2 mg/kg of isosorbide-5-mononitrate would be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin would require even larger doses of isosorbide-5-mononitrate.

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 pO2. Classically, methemoglobinemic blood is described as chocolate brown without colour change on exposure to air. When methemoglobinemia is diagnosed, administration of methylene blue, 1 to 2 mg/kg intravenously, may be required.

For management of a suspected drug overdose, contact you regional Poison Control Center Immediately

DOSAGE AND ADMINISTRATION

Dom-ISMN (isosorbide-5-mononitrate), administered once daily, provides efficacy for up to 12 hours. This formulation is designed to avoid or attenuate the development of tolerance.

The recommended starting dose of Dom-ISMN, for those patients who are active during the day, is 60 mg (one tablet) once daily to be taken in the morning on arising. The dose may be increased to 120 mg (two tablets) once daily. Rarely 240 mg may be required. To minimize the possibility of headache the dose can be titrated by initiating treatment with 30 mg (half a tablet) for the first 2-4 days.

Dosage adjustments are not necessary for elderly patients or patients with altered renal or hepatic function.

The tablet may be taken whole or as divided halves.

The tablets should not be chewed or crushed, and should be swallowed together with half a glass of water. Whole tablets may sometimes seem to appear in the stool; these will only be the matrices which have remained intact after the active substance has been leached out.

NOTE: Dom-ISMN is not indicated for the relief of acute anginal attacks; in these situations sublingual or buccal nitroglycerin should be used.

STORAGE AND STABILITY

Store between 15 °C and 30 °C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

Dom-ISMN are extended release, yellow, oval, biconvex, film coated tablets in the strength of 60 mg. The tablet is scored on both sides and debossed with "P" on one side of the scored line only on one side of the tablet.

The tablets are available in compliance blister packs, 30 tablets/pack, and in bottles of 100 tablets.

Composition

Dom-ISMN Tablets contain 60 mg isosorbide-5-mononitrate. The tablets also contain the following non medicinal ingredients (alphabetically): colloidal silicon dioxide, hydroxypropyl methylcellulose, iron oxide yellow, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide.

PHARMACEUTICAL INFORMATION

Drug Substance

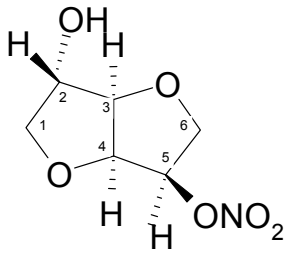
Proper name: Isosorbide-5-mononitrate

Chemical Name: D-glucitol,1,4:3,6-dianhydro-, 5-nitrate

Molecular Formula: $C_6H_9NO_6$

Molecular Weight: 191.14 g/mol

Structural Formula:



Physicochemical properties: White to yellowish-white, crystalline powder or fine needles. Freely soluble in water, ethanol (99.5%) and dichloromethane. Specific optical rotation $[\alpha]_D20$: about +144° (0.5% aqueous solution). Melting point about 90°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-dose, 2-way crossover, blind, randomized, comparative bioavailability study of Dom-ISMN 60 mg Extended Release Tablets, manufactured by Dominion Pharmacal ., was performed versus IMDUR®, manufactured by AstraZeneca Canada Inc. and administered as 1 x 60 mg Tablet in 22 healthy male volunteers in the fasting state. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Isosorbide-5-mononitrate (1 x 60 mg ER tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Dom-ISMN	IMDUR[†]	% Ratio of Geometric Means±	Confidence Interval± (90%)
AUC_T (ng·h/mL)	6071.17 6140.65 (16.18)	6553.64 6577.73 (11.29)	92.64	86.30 – 99.44
AUC_I (ng·h/mL)	6205.21 6275.17 (16.11)	6726.18 6757.39 (12.17)	92.25	86.12 – 98.83
C_{max} (ng/mL)	449.01 452.38 (12.69)	439.36 441.02 (10.16)	102.20	96.86 – 107.82
T_{max}[§] (h)	4.50 (2.00 – 5.50)	4.50 (3.50 – 6.00)		
$T_{½}$[€] (h)	5.92 (20.97)	6.13 (14.02)		

[†] Imdur® was manufactured by AstraZeneca, Canada and was purchased in Canada
[§] Expressed as the median (range) only
[€] Expressed as the arithmetic mean (CV%) only
± Comparisons were made on the least squares mean estimate as the study was unbalanced

A single-dose, 2-way crossover, blind, randomized, comparative bioavailability study of Dom-ISMN 60 mg Extended Release Tablets, manufactured by Dominion Pharmacal . was performed versus IMDUR®, manufactured by AstraZeneca Canada Inc. and administered as 1 x 60 mg Tablet in 22 healthy male volunteers in the fed state. Bioavailability data were measured and the results are summarized in the following table:

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Parameter	Dom-ISMN	IMDUR†	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng·h/mL)	7059.41 7131.26 (14.31)	6678.45 6760.65 (15.83)	105.70	102.16 – 109.38
AUC_I (ng·h/mL)	7182.99 7258.41 (14.55)	6812.22 6899.11 (16.07)	105.44	101.77 – 109.25
C_{max} (ng/mL)	501.75 506.29 (14.12)	451.45 459.18 (19.08)	111.14	104.08 – 118.68
T_{max}§ (h)	4.75 (4.00 – 8.00)	5.00 (4.00 – 8.00)		
$T_{½}$€ (h)	5.36 (11.40)	5.51 (10.57)		

† Imdur® was manufactured by AstraZeneca, Canada and was purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

INFORMATION FOR THE CONSUMER

(for Compliance Blister Pack)

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT
Dom-ISMN

Read this leaflet carefully. It has been prepared by the makers of Dom-ISMN to help you get the most benefit from this drug. It contains general points about Dom-ISMN and should add to more specific advice from your doctor or pharmacist.

This leaflet should not replace your doctor's or pharmacist's advice. Because of your health condition, they may have given you additional instructions. If so, be sure to follow their advice. Also, if you have any questions or concerns after reading this leaflet, talk to your doctor or pharmacist. **Do not decide on your own to stop taking** Dom-ISMN**.**

WHAT IS Dom-ISMN?

Dom-ISMN is the brand name for the extended release formulation of isosorbide-5-mononitrate, which is released gradually over a 10 hour period. Dom-ISMN belongs to a family of drugs called nitrates that function by dilating blood vessels.

Dom-ISMN is used to prevent severe chest pain and feeling of pressure around the heart (recurring angina pectoris). Dom-ISMN is not intended for the immediate relief of sharp chest pains (acute angina pectoris).

WHAT SHOULD I TELL MY DOCTOR BEFORE STARTING Dom-ISMN?

Be sure you've told your doctor:
- about all health problems you have now, and have had in the past;
- about all other medicines you take, including any you take for high blood pressure, and ones you can buy without a prescription;
- if you are pregnant, plan to become pregnant, or are breast feeding;
- if you have ever had an allergic, bad or unusual reaction to nitrates or to any medicine for heart problems;
- if you are allergic to non-medicinal substances like food products, preservatives, or dyes, which may be present in Dom-ISMN (see What Does Dom-ISMN Contain?).

WHAT DOES Dom-ISMN CONTAIN?

Most medicines contain more than their "active" ingredient. These other ingredients are needed to keep medicines in a form you can use. For people with certain allergies, the following is a list of all ingredients in Dom-ISMN. Check with your doctor if you think you might be sensitive to any of these items.

The active ingredient in Dom-ISMN is isosorbide-5-mononitrate. Non-medicinal ingredients are: colloidal silicon dioxide, hydroxylpropyl methylcellulose, iron oxide yellow, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide.

HOW DO I USE THE Dom-ISMN COMPLIANCE PACK?

To help you keep track of your doses, Dom-ISMN comes in a blister pack with days of the week printed on the back of the blister. Start with the tablet that matches the day of the week and continue taking them in order until they are all finished.

There are 28 days of labeled tablets in each blister, with two extra to make 30. All 30 tablets, including the two labeled "last two days", are exactly the same. Once you have finished the 28 labeled tablets, take the two marked "Last two days", for the following two days, before starting your next blister pack.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken. This unique 30 day package is designed to make it easy to keep track of your medication.

HOW DO I TAKE Dom-ISMN?

Take Dom-ISMN exactly as your doctor tells you. Usually, this is one tablet in the morning. If your doctor tells you to take two tablets each day, they must be taken together in the morning. Check with your doctor or pharmacist if you have any questions about your directions.

Dom-ISMN tablets should be swallowed whole, with half a glass of water or other liquid e.g., fruit juice or milk. **Do not chew or crush the tablets.**

If needed, the tablets may be broken in half along the scored line.

Do not take extra doses of Dom-ISMN, unless your doctor tells you. Using more can increase the chance of unwanted effects.

WHAT DO I DO IF I MISS A DOSE?

It is important to take Dom-ISMN at about the same time every day.

If you miss a dose of Dom-ISMN and remember within 6 hours, take your usual dose as soon as possible. Then go back to your regular schedule. But if it is more than 6 hours when you remember, do not take the missed dose. Just take the next dose on time.

Never take a double dose of Dom-ISMN to make up for missed tablets. If you are still unsure, check with your doctor or pharmacist to see what you should do.

WHAT ARE THE SIDE EFFECTS OF Dom-ISMN?

Dom-ISMN, like any medication, may produce side effects.

The most common side effect is headache. It often occurs at the beginning of the treatment, but usually goes away after a few days. If you get a bad headache, and it becomes a problem, be sure to tell your doctor.

If too much Dom-ISMN is taken, a severe pulsing headache might occur. You may feel lightheaded, dizzy, excited, flushed, have cold sweats, nausea (feeling sick) and vomiting. If any of these symptoms occur, lie down with your feet raised and get someone to call your doctor right away.

Some people feel Dom-ISMN makes them dizzy, faint, or tired. This is more likely when Dom-ISMN is first started. If you have any of these effects, please tell your doctor.

Do not stop taking Dom-ISMN until your doctor tells you. He or she may want to reduce your dose slowly.

Remember, medicines affect different people in different ways. Just because other people have had side effects does not mean you will get them. Discuss how you feel on Dom-ISMN with your doctor or pharmacist.

Other side effects which cannot be predicted may occur in rare cases. If you have any bothersome or unusual effects while using Dom-ISMN, check with your doctor or pharmacist right away.

ARE THERE ANY SPECIAL PRECAUTIONS?

If you are taking Dom-ISMN, you must not take phosphodiesterase type 5 inhibitors (i.e. Viagra® (sildenafil), Cialis® (tadalafil), Levitra® (vardenafil)). Such a combination can produce severe lowering of blood pressure, loss of consciousness, heart attack, or death.

Unused medicines which you know you will no longer need should be carefully discarded. Small quantities may be disposed of in the toilet or you may wish to seek advice from your pharmacist.

The Compliance Pack protects each tablet. When you first open the pack, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.

HOW DO I STORE Dom-ISMN?

Although Dom-ISMN tablets are protected in this Compliance Pack, it is best to keep it at normal room temperature and in a dry place. Do not keep Dom-ISMN in the bathroom. Do not keep or use Dom-ISMN after the expiry date marked on the Compliance Pack.
Do not transfer Dom-ISMN to other containers. To protect your Dom-ISMN tablets, keep them in the original Compliance Pack.

Keep Dom-ISMN out of the reach of children. Never take medicine in front of small children as they may want to copy you.

GENERAL INFORMATION

Dom-ISMN is for your current condition only. Do not use it for other problems unless your doctor tells you. Never give it to other people to use.

Be sure to tell your doctors, dentists and pharmacists that you take Dom-ISMN.

All drugs can have both helpful and harmful effects. Both depend on the person and his or her health condition. This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor with any questions or concerns you have about Dom-ISMN.

REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

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PHARMACOLOGY

Animal

Pharmacodynamics

The primary pharmacological effect of isosorbide-5-mononitrate was identified to be relaxation of the vascular smooth muscle. It is likely that the vasodilating property of isosorbide-5-mononitrate is due to stimulation of guanylate cyclase, leading to an increase in cGMP and a decrease in the free, intracellular Ca2+ concentration.

Studies in the rabbit have demonstrated that the vasodilating property of isosorbide-5-mononitrate is 100 times more potent in the vena cava than in the aorta and that isosorbide-5-mononitrate was more potent in relaxing isolated renal and femoral veins than the corresponding arteries. Further studies have indicated that isosorbide-5-mononitrate has a capacity to dilate venous smooth muscle at lower concentrations than are needed for arterial smooth muscle.

In conscious dogs, injections of isosorbide-5-mononitrate produced a decrease in stroke volume, a decrease in maximum dP/dt and a reduction of the systolic arterial pressure. The diastolic pressure remained unchanged. The mechanism for these changes is increased venous capacitance reducing the pre-load and thus reducing volume and contractility. The low stroke volume caused a fall in systolic blood pressure. In addition, the after-load was reduced by a diminished aortic impedance. Another study in conscious dogs also showed that at low dose not only venous capacitance vessels, but also conductance arteries are dilated. Much higher doses were required to decrease peripheral and coronary resistance. Minimal plasma concentrations required to affect systolic blood pressures have been estimated as low as 30 ng/mL. These studies show that at therapeutic plasma concentrations of isosorbide-5-mononitrate, the hemodynamic effects of the drug include dilation of venous capacitance, but not arterial resistance vessels.

Isosorbide-5-mononitrate does not exert significant effects on the rabbit myocardium when studied in left atrial preparations. Concentrations of isosorbide-5-mononitrate several thousand times greater than plasma levels in man did not affect force-frequency relationships over the range 10-400 beats/min.

Isosorbide-5-mononitrate has beneficial effects on myocardial ischemia. Conscious dogs, with ischemia induced by occlusion of a coronary artery, were treated with 20 mg and 40 mg isosorbide-5-mononitrate. There was a significant lowering of the ST-segment elevations during treadmill exercise.

TOXICOLOGY

Acute Toxicity

Table 1

Species	Route	Sex	LD_{50}		Time
			mmol/kg	mg/kg	
mouse	p.o.	M	> 16	> 3100	1 day
			11 (10–12)	2100 (1900–2200)	14 days
mouse	p.o.	M	> 10	> 1900	14 days
	p.o.	F	> 10	> 1900	14 days
mouse	i.v	M	8.5-11	1600	14 days
	i.v	F	11-15	2100	14 days
rat	p.o.	M	11 (10-12)	2100 (1900–2200)	1 + 14 days
rat	p.o	M	8.3 (6.8-10)	1600 (1300-1900)	14 days
	p.o	F	7-8.4	1340-1610	14 days
rat	i.v.	M	> 6	> 1100	14 days
	i.v.	F	> 6	> 1100	14 days

Signs of acute toxicity in the mouse and rat were lethargy, coma, lacrimation, cyanosis and irregular breathing.

Signs of acute toxicity after oral administration to dogs were hyperemia at 128 and 256 mg/kg (670 and 1430 µmol/kg), somnolence at 256 mg/kg (1340 µmol/kg), apathy and ataxia at 384 mg/kg (2010 µmol/kg). The dogs seemed to have recovered 6 hours after dosing. The maximally tolerated dose was 256 mg/kg (1340 µmol/kg).

General Toxicity After Repeated Administration

Toxicity after repeated administration has been studied in rats and dogs after 26 weeks of oral administration.

Rats were treated with doses of 0, 15, 60 or 250 mg/kg isosorbide-5-mononitrate for 26 weeks. There were 25 male and 25 female rats in each dose group. Mean weekly body weights at weeks 13 and 26 and body weight gains from initiation to weeks 13 and 26 were significantly decreased in the high-dose males (250 mg/kg). Only mean terminal body weight was significantly decreased in the high-dose females. There were several transient changes in hematology and clinical chemistry parameters noted at week 6, but at termination all hematology and clinical chemistry variables were similar between groups of the same sex. Clinical signs, ophthalmological findings, food consumption, organ weight changes and gross and microscopic pathology findings were considered incidental and not related to treatment.

The 26-week study on dogs was performed on 40 beagles receiving 0, 5, 20 or 60 mg/kg isosorbide-5-mononitrate. There were 5 male and 5 female dogs in each dose group. Although no statistically significant differences were noted, mean body weights along with mean total food consumption were slightly increased in a dose-related manner in the males and females. No consistent or dose-related changes were noted in clinical signs, ophthalmological findings, ECG findings, organ weight data, clinical pathology data, gross and microscopic pathology.

Teratogenicity

Female rats were treated with 0, 9.6, 48 and 240 mg/kg isosorbide-5-mononitrate on days 6-15 of pregnancy (20 rats/group). On day 21 the dams were killed. There were no signs of adverse effects on either the dams or fetuses related to isosorbide-5-mononitrate.

Rabbits were treated with 0, 15, 57 and 248 mg/kg isosorbide-5-mononitrate on days 6-19 of gestation (20 rabbits/group). On day 29 the females were killed. There were no adverse effects on pregnant rabbits or fetuses that could be related to treatment with isosorbide-5-mononitrate.

Mutagenicity

No mutagenic properties of isosorbide-5-mononitrate were found in Ames test, mouse micronucleus test and chromosome aberration test in human lymphocytes. A weak effect at high concentrations of isosorbide-5-mononitrate was found in the mouse lymphoma test. However, considering the occurrence of similar effects of other chemicals at high concentrations, supposedly via non-specific mechanisms, the mutagenic activity seen with isosorbide-5-mononitrate in this very sensitive test system is judged as biologically insignificant.

Carcinogenicity

The carcinogenic potential of isosorbide-5-mononitrate was studied in rats after administration in the diet for 125 weeks (males) and 138 weeks (females). Dose levels were 70, 245 and 900/500 mg/kg (50 male and 50 female rats per group). The high dose was reduced to 500 mg/kg from test week 26 onward due to inhibited body weight gain.

Male rats in the 245 mg/kg dose group had a slightly inhibited body weight gain from test week 25 onwards. The difference from controls was maximally 6% in test week 39. Food consumption of the female rats receiving 70 and 245 mg/kg was lower than for the female control rats from test week 9 to test week 82 (maximally 12-15% in test weeks 23-25). The females on 900/500 mg/kg showed an increased food consumption (maximally + 18% in test week 91) after lowering the dose to 500 mg/kg.

Clinical signs, water intake, hematology, ophthalmoscopic examination, inspection of hearing and dentition did not indicate any influence caused by the test compound.

On macroscopic examination, no masses were seen in the dosed groups which deviated from the control group. Microscopical examination of treated rats, restricted to those which were given 245 and 900/500 mg/kg and controls, revealed tumours in all groups. The tumour rates (percentage of tumour-bearing animals) of the medium and high dosed animals as well as the control rats were very close and showed no indications of substance-related neoplastigenic properties. Tumours and pathological lesions in both treated and untreated animals showed a profile normal to Sprague-Dawley rats with respect to nature, localization and time of

appearance. The ratio of benign to malignant neoplasms was within the normal range of the strain. Examinations revealed no tumours in the nasal region of any animal.

In conclusion, isosorbide-5-mononitrate has no apparent carcinogenic effects under the conditions of testing.

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