PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ISDN

Isosorbide Dinitrate Tablets

5 mg (sublingual), 10 mg and 30 mg (oral)

USP

Coronary Vasodilator

AA PHARMA INC.
1165 Creditstone Road Unit #1
Vaughan, Ontario
L4K 4N7
www.aapharma.ca/en/

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ISDN (isosorbide dinitrate tablets) is indicated for:

- Prophylaxis of ischemic heart pain associated with coronary insufficiency. ISDN may reduce the number, duration and severity of anginal attacks; exercise tolerance may be increased and nitroglycerin requirements curtailed.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

ISDN (isosorbide dinitrate tablets) is contraindicated in:

- Patients who are hypersensitive to isosorbide dinitrate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who are taking phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and vardenafil. PDE5 inhibitors may amplify the vasodilatory effects of ISDN which can lead to severe hypotension.
- Patients who are taking the soluble guanylate cyclase stimulator riociguat. Concomitant use can cause hypotension.

Although ISDN may be used for the control of angina pectoris occurring after myocardial infarction, it is suggested that treatment be withheld in the presence of cardiogenic shock, or if there is a risk of shock developing.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Dosing regimens should account for the possible development of tolerance to ISDN and cross tolerance to other nitrates and nitrites.

Multiple-dose studies with isosorbide dinitrate and other nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. A daily dose-free interval is advisable to minimize tolerance. The optimal interval will vary with the individual patient, dose and regimen. See 7 WARNINGS AND PRECAUTIONS, Dependence, Tolerance and/or Abuse Liability.

4.2 Recommended Dose and Dosage Adjustment

Sublingual Administration (tablets dissolve in 20 seconds in the mouth)

5 to 10 mg sublingually (1 to 2 sublingual 5 mg tablets), every 2 to 4 hours for the prophylaxis of acute angina; may be supplemented by a dose of 5 to 10 mg sublingually prior to stressful situations likely to provoke an attack of angina.

Oral Administration

20 to 120 mg daily in divided doses, according to therapeutic and patient response.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

4.4 Administration

The 5mg ISDN sublingual tablet should be placed under the tongue, and will dissolve in approximately 20 seconds.

The 10 mg and 30 mg ISDN oral tablets should be swallowed whole with a glass of water.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5 OVERDOSAGE

Hemodynamic Effects

The ill effects of isosorbide dinitrate overdose are generally the results of isosorbide dinitrate'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 dinitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide dinitrate overdose.

There are no data suggesting what dose of isosorbide dinitrate is likely to be life-threatening in humans. In rats, the median acute lethal dose (LD_{50}) was found to be 1100 mg/kg.

No data are available to suggest physiological maneuvers (*e.g.*, maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide dinitrate and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of isosorbide dinitrate is known, and no intervention has been subject to controlled studies as a therapy for isosorbide dinitrate overdose. Because the hypotension associated with isosorbide dinitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward 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 dinitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate 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 dinitrate. 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 4.8 to 6.9 mg of bioavailable isosorbide dinitrate 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Sublingual (5 mg) and oral (10 mg, 30 mg)	Tablets 5 mg, 10 mg, and 30 mg of isosorbide dinitrate	Colloidal silicon dioxide (5 mg and 30 mg tablets only), croscarmellose sodium, D&C Red #30 AL Lake (5 mg tablets only), lactose monohydrate, magnesium stearate and microcrystalline cellulose

ISDN 5 mg Sublingual: Each pink, round, flat-faced, bevelled-edge tablet, engraved 5 on one side, other side plain, contains 5 mg of isosorbide dinitrate. Available in bottles of 100 and 500.

ISDN 10 mg Oral: Each white, round tablet, bevelled-edge and flat one side, convex on other. Engraved score over 10 on flat side, convex side plain, contains 10 mg of isosorbide dinitrate. Available in bottles of 100 and 1000, unit dose packages of 100 (10x10s).

ISDN 30 mg Oral: Each white, round tablet, bevelled-edge and flat one side, convex on other. Engraved score over I30 on flat side, convex side plain , contains 30 mg of isosorbide dinitrate. Available in bottles of 100 and 1000, unit dose packages of 100 (10x10s).

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction or congestive heart failure, (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia. Because the effects of oral isosorbide dinitrate are so difficult to terminate rapidly, this formulation is not recommended in these settings.

Amplification of the vasodilatory effects of ISDN 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.

Isosorbide dinitrate is a potent vasodilator and causes a slight decrease in mean blood pressure (approximately 10 to 15 mm Hg) in some patients when used in therapeutic doses. Caution should be exercised in using the drug in patients who are prone to, or might be affected by, hypotension.

Hypotension induced by isosorbide dinitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Dependence, Tolerance and/or Abuse Liability

Tolerance to this drug and cross tolerance to other nitrites and nitrates may occur.

As tolerance to isosorbide dinitrate develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24-hour day. During the daily dose-free interval in some of these trials, anginal attacks have been more easily provoked than before treatment, and patients have demonstrated hemodynamic rebound and decreased exercise tolerance. The importance of these observations to the routine, clinical use of immediate-release oral isosorbide dinitrate tablets is not known.

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.

Driving and Operating Machinery

Dizziness, fatigue or blurred vision might occur at the start of treatment. Exercise caution when driving or operating machinery.

Ophthalmologic

Use ISDN with caution in patients with glaucoma.

Renal

In patients with renal insufficiency, ISDN should be used with caution since the hypotensive effect may cause a dangerous reduction in renal blood flow.

7.1 Special Populations

7.1.1 Pregnant Women

At oral doses 35 and 150 times the maximum recommended human daily dose, isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in

mummified pups) in rabbits. There are no adequate, well-controlled studies in pregnant women. ISDN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is unknown if isosorbide dinitrate is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

Clinical studies of isosorbide dinitrate 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions to isosorbide dinitrate are generally dose-related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator.

As with nitroglycerin and other nitrates, vascular headache occurs and ~~it~~ may be severe and persistent. This adverse effect occurs most frequently at the beginning of therapy. Headache usually can be controlled by temporary dosage reduction, concomitant administration of suitable analgesics or by administering the drug during meals. These headaches usually disappear within 1 week of continuous, uninterrupted therapy. It is usually best to advise the patient of their possible occurrence and of their importance in regard to the prevention of angina. Drug and/or exfoliative dermatitis occasionally occur. Signs of cerebral ischemia associated with postural hypotension such as weakness, transient episodes of dizziness may occasionally develop. Cutaneous vasodilatation with flushing may occur. Rarely a marked sensitivity to the hypotensive effects of the drug and severe response (nausea, vomiting, restlessness, perspiration and collapse) can occur and alcohol may enhance this effect.

Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred. See 5 OVERDOSAGE.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant use of ISDN (isosorbide dinitrate tablets) with phosphodiesterase type 5 (PDE5) inhibitors such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and vardenafil can potentiate the hypotensive effect of ISDN. This could result in life-threatening hypotension with syncope or myocardial infarction and death. Therefore, PDE 5 inhibitors should not be given to patients receiving ISDN therapy. See 2 CONTRAINDICATIONS.
- Concomitant use of ISDN with riociguat, a soluble guanylate cyclase stimulator, is contraindicated due to the risk of hypotension. See 2 CONTRAINDICATIONS.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Blood pressure lowering agents, including alcohol	T	The vasodilating effects of isosorbide dinitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.	
Histamine or epinephrine, acetylcholine	T	ISDN can antagonize the effects of histamine or epinephrine, acetylcholine and similar agents.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phosphodiesterase type 5 (PDE 5) inhibitors	T	Potentiation of the hypotensive effect result in life-threatening hypotension with syncope or myocardial infarction and death.	Concomitant use with ISDN is contraindicated.
Riociguat, a soluble guanylate cyclase stimulator	T	Risk of hypotension.	Concomitant use with ISDN is contraindicated.

Legend: T=Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The basic action of isosorbide dinitrate is the relaxation of smooth muscle. Relaxation of peripheral vascular smooth muscle and peripheral pooling of blood results in the reduction of preload and afterload on the left ventricle. The effect of the long acting nitrate appears to be mainly peripheral. Although isosorbide dinitrate dilates the coronary arteries there is no incontrovertible evidence that it relieves ischemic heart pain by increasing coronary blood flow.

10.2 Pharmacodynamics

Isosorbide dinitrate dilates vascular smooth muscle throughout the body. It exerts its strongest effect on the venous system and a lesser effect on the arterial circulation.

Mason et al., studied the peripheral circulatory actions of nitroglycerin in normal human volunteers. Mean arterial pressure declined slightly, forearm blood flow increased, the calculated forearm vascular resistance decreased by a mean of 35% and venous tone declined by an average of 19%. The changes in all four variables were statistically significant.

Gensini et al. measured the changes in coronary vascular diameter of dogs following the isosorbide dinitrate administrations of 1 mg intracutaneously, 2 mg intravenously, 40 mg orally in the form of crushed tablets, and 40 mg in the form of intact tablets. The intracutaneous and intravenous administration of the drug produced a mean coronary vasodilation of 7%, the effects of the intravenous administration dissipating somewhat faster than those following the intracutaneous administration. Vasodilation was also clearly measurable after the oral administrations of the drug, although the effects were more pronounced with the crushed tablets.

As with other nitrates, the precise mechanism of action of isosorbide dinitrate on the smooth muscle cells of blood vessels has not been determined. It appears that isosorbide dinitrate and related compound acts on the specific nitrate receptor site in the vascular wall and react with sulfhydryl group producing a nitrite ion which is a generalized smooth muscle relaxant.

Needleman et al. showed that incubating rabbit aortic strips with glyceryl trinitate at alkaline pH resulted in the formation of nitrite ions and a net loss of titratable sulfhydryl. A direct relationship between tissue contractibility and sulfhydryl groups present was also demonstrated.

Nitrate tolerance was induced *in vitro* by incubating aortal strips with glyceryl trinitrate. This tolerance was reversible by disulfide reducing agents, demonstrating that the oxidation of the sulfhydryl receptor site is the cause of the reduced effectiveness of the nitrates. The same results were obtained when tolerance was developed *in vivo* in rats (100 mg/kg t.i.d., 3 days). Thoracic aortas from the nitrate-tolerant animals showed an approximately 500-fold shift *in vitro* glyceryl trinitrate sensitivity, but could be returned to near normal sensitivity by treatment with dithiothreitol.

10.3 Pharmacokinetics

Absorption

After oral administration ISDN appears to be rapidly absorbed, with relief of angina pectoris beginning in 30 minutes and lasting 4 to 6 hours.

When administered sublingually, ISDN absorbs rapidly and essentially completely. Isosorbide dinitrate tablets taken sublingually have an onset of action of 2 to 5 minutes and last 1 to 2 hours.

Distribution

Equilibrium dialysis experiments suggest that isosorbide dinitrate is not extensively bound to plasma proteins. According to a one study, the disposition of isosorbide dinitrate showed a clear bi-exponential characteristic with half lives of approximately 1.5 and 4 hours for the alpha and beta phases, respectively. According to this study, plasma isosorbide dinitrate concentrations after chronic dosing were in general higher than those obtained after the comparable single doses.

Metabolism

Isosorbide dinitrate is metabolized to 2-isosorbide mononitrate (2-ISMN) and 5-isosorbide mononitrate (5-ISMN).

Nitrates are rapidly metabolized in the liver by glutathion reductase. Some investigations indicate that there is a wide interindividual variation in the pharmacokinetics of isosorbide dinitrate and that some of the metabolites are also active. Two- and 5-isosorbide mononitrate were found to exert a lesser but longer lasting hemodynamic effect than isosorbide dinitrate.

Thus, the active metabolites may contribute to the duration of action of isosorbide dinitrate.

Elimination

After a single oral dose, 80 to 100% of the amount absorbed is excreted in the urine within 24 hours, chiefly as metabolites.

Studies show that elimination follows 1st order kinetics (1 compartment model) with a half life of about 30 minutes.

Elimination occurs via the urine and is practically 100% within 24 hours post-administration. Intact isosorbide dinitrate is not found in urine. Twenty to 30% of the dose is excreted as 5-ISMN, 2-ISMN, isosorbide and isoiodide. The remainder is excreted primarily as the ether glucuronide of 5-ISMN and isosorbide.

Special Populations and Conditions

- **Pediatrics:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatrics:** 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.
- **Renal Insufficiency:** In patients with renal insufficiency, ISDN should be used with caution.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

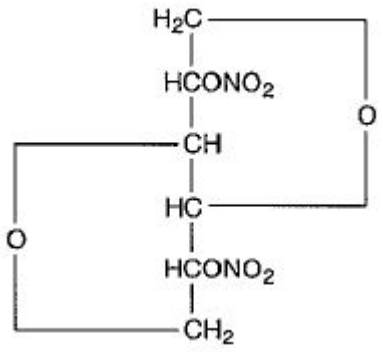
Drug Substance

Proper/Common Name: isosorbide dinitrate

Chemical Name: D-Glucital, 1,4:3,6-dianhydro-, dinitrate

Molecular Formula and molecular mass: $C_6H_8N_2O_8$ and 236.14 g/mol

Structural Formula:



Physicochemical properties: Isosorbide dinitrate is a white, crystalline odourless compound. It is sparingly soluble in water, and is freely soluble in acetone, ether, and alcohol. It has a melting point of 70°C and optical rotation of +134 (c=1.0, alcohol, 20°C).

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Following the oral administration of the drug in rats, the acute LD_{50} was found to be approximately 1100 mg/kg of body weight.

Chronic oral toxicity was determined in rats and dogs. The following dosage levels were employed in the chronic toxicity studies:

Rats: 100 mg/kg, 50 mg/kg, 25 mg/kg, and control. Dogs: 100 mg/kg, 50 mg/kg, 25 mg/kg, and control.

Male rats and dogs at the highest dosage level showed a decrease in growth curve as compared to control animals and animals in the lower dosage groups. Histological examination of the tissues did not reveal evidence of toxic injury. There was no evidence of an effect on bone marrow, the hematopoietic system or the peripheral blood. Examination of blood samples in dogs for the presence of methemoglobin failed to reveal a significant level of the pigment.

Carcinogenicity:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of isosorbide dinitrate.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ISDN

Isosorbide Dinitrate Tablets

Read this carefully before you start taking **ISDN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ISDN**.

What is ISDN used for?

ISDN is used in adults to prevent chest pain (angina) caused by too little blood and oxygen getting to the heart muscle.

How does ISDN work?

ISDN belongs to a group of medicines called nitrates. It relaxes and widens your blood vessels, which lets more blood and oxygen reach the heart muscle.

What are the ingredients in ISDN?

Medicinal ingredients: Isosorbide dinitrate

Non-medicinal ingredients: Colloidal silicon dioxide (5 mg and 30 mg tablets only), croscarmellose sodium, D&C Red #30 AL Lake (5 mg tablets only), lactose monohydrate, magnesium stearate and microcrystalline cellulose.

ISDN comes in the following dosage forms:

Sublingual tablets: 5 mg.

Oral tablets: 10 mg and 30 mg.

Do not use ISDN if:

- you are allergic to isosorbide dinitrate, to any other nitrate medicines or to any of the other ingredients in this medicine.
- you are taking medicines known as phosphodiesterase type 5 inhibitors. This includes

erectile dysfunction medications such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and vardenafil. Taking one of these medicines with ISDN may cause a dangerous fall in blood pressure and result in collapse, unconsciousness and could be fatal.
- you are taking riociguat (a medicine used to treat high blood pressure in the lungs). If you are unsure, ask your healthcare professional.
- you have cardiogenic shock (your heart is not delivering enough oxygen around your body).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ISDN. Talk about any health conditions or problems you may have, including if you:

- have recently had a heart attack or stroke.
- have congestive heart failure.
- have low blood pressure.
- have been taking any nitrate or nitrite medicines similar to ISDN.
- have an eye disease called glaucoma.
- have kidney problems.
- have lactose intolerance.
- are pregnant, think you are pregnant, or planning to be pregnant.
- are breastfeeding.

Other warnings you should know about:

Tolerance: If you take ISDN continuously throughout the day for a certain period of time, you may build up a tolerance to it, or other nitrates and nitrites. To try and prevent tolerance, your healthcare professional may advise you not to take any ISDN for a certain number of hours ("ISDN-free period") each day.

Driving and using machines: ISDN may cause dizziness, fatigue, or blurred vision. Give yourself time after using ISDN to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions:

Do **NOT** take ISDN with:

- medicines known as phosphodiesterase type 5 inhibitors. This includes erectile dysfunction medications such as VIAGRA® (sildenafil), CIALIS® (tadalafil) and vardenafil.
- riociguat, a medicine used to treat high blood pressure in the lungs.

The following may also interact with ISDN:

- Epinephrine, used in emergencies to treat very serious allergic reactions.
- Acetylcholine, used for eye surgeries, activate skeletal muscles.
- Medications used to lower blood pressure.
- Alcohol.

How to take ISDN:

- Follow the directions given to you by your healthcare professional.

Sublingual Tablets

- ISDN sublingual tablet is absorbed through the lining of your mouth.
- Place your ISDN tablet under your tongue, or in your cheek and allow to dissolve.
- Tablets will dissolve in 20 seconds in the mouth.
- Do NOT chew, crush or swallow your ISDN tablet whole, as swallowed sublingual tablets are NOT effective.
- While the tablet is dissolving, avoid eating, drinking or smoking until the tablet has completely dissolved.

Oral Tablets

- Swallow ISDN oral tablets whole with a glass of water.
- Do not chew or crush the tablets.

Usual dose:

Sublingual Tablets: 5 to 10 mg sublingually (1 to 2 sublingual 5 mg tablets), every 2 to 4 hours for the prevention of short-term chest pain; may be supplemented by a dose of 5 to 10 mg sublingually prior to stressful situations likely to provoke an attack of angina.

Oral Tablets: 20 to 120 mg daily, in divided doses as recommended by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much ISDN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at the regular scheduled time. Do NOT double your dose to make up the missed dose.

What are possible side effects from using ISDN?

These are not all the possible side effects you may have when taking ISDN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- light-headedness
- dizziness
- weakness
- flushing of the face
- nausea or vomiting
- restlessness
- sweating

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Rebound hypertension (sudden increase in blood pressure when a person stops taking certain medications): headache, fast heart rate of over 100 beats per minute (bpm), nausea, flushed skin, warm feeling, tightness in the chest, tremors, anxiety, nervousness, difficulty seeing		√	
Syncope (fainting and passing out)		√	
Unstable angina (worsening chest pain) that occurs with less exertion, and lasts longer than stable angina			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Cerebral ischemia (not enough blood flow to the brain): sudden weakness, difficulty speaking, blurred vision, dizziness, confusions, loss of conciousness			√
Collapse		√	
Exfoliative dermatitis (severe skin reaction): red, scaly and peeling skin	√		
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
VERY RARE			
Methemoglobinemia (a type of blood disorder): headache, nausea, dizziness, fatigue, shortness of breath, blue coloured skin, fast heart rate, chocolate-coloured blood		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15°C to 30°C.

Protect from moisture.

Keep out of reach and sight of children.

If you want more information about ISDN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc. 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

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