ISOSORBIDE DINITRATE- isosorbide dinitrate tablet
West-ward Pharmaceutical Corp

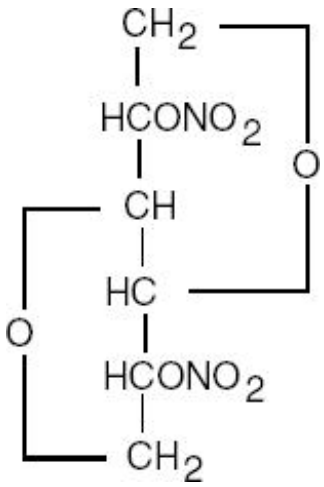
ISOSORBIDE DINITRATE SUBLINGUAL TABLETS, USP

Rev 11/07

Rx Only

DESCRIPTION

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins.

ISDN is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of 70°C and has an optical rotation of +134° (c=1.0, alcohol. 20°C). ISDN is freely soluble in organic solvents such as acetone, alcohol, and ether, but is only sparingly soluble in water.

Each isosorbide dinitrate sublingual tablet contains 2.5 mg or 5 mg of ISDN.

Inactive ingredients are as follows:

2.5 mg Sublingual: Ammonium phosphate dibasic, anhydrous lactose, colloidal silicon dioxide, corn starch, D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

5 mg Sublingual: Ammonium phosphate dibasic, anhydrous lactose, colloidal silicon dioxide, corn starch, magnesium stearate, microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The principal pharmacological action of ISDN is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular lesistance, 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.

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 anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate 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 anti-anginal efficacy been restored.

Pharmacokinetics

Bioavailability of ISDN after single sublingual doses is 40 to 50%. Multiple-dose studies of sublingual ISDN pharmacokinetics have not been reported; multiple-dose studies of ingested ISDN have observed progressive increases in bioavailability during chronic therapy. Serum levels of ISDN reach their maxima 10 to 15 minutes after sublingual dosing.

Once absorbed, the distribution volume of ISDN is 2 to 4 L/kg, and this volume is cleared at the rate of 2 to 4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is affected primarily by denitration to the 2-mononitrate (15 to 25%) and the 5-mononitrate (75 to 85%).

Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.

The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10 to 12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (*e.g.*, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.

Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had *less* exercise tolerance at the end of the daily dose-fiee interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.

Clinical trials

In a controlled trial in which 0.4 mg of sublingual nitroglycerin took 1.9 minutes to begin to produce an anti-anginal effect, 5 mg of sublingual ISDN took 3.4 minutes to begin to produce a similar effect. In the same trial, the anti-anginal effect of the sublingual nitroglycerin was evident for about an hour, while that of the sublingual ISDN lasted about 2 hours.

In other controlled trials, the anti-anginal efficacy of sublingual ISDN has persisted for periods ranging from 30 minutes up to 4 hours.

Multiple-dose trials of sublingual ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen includes a dose-free interval of at least 14 hours. The daily dose-free interval necessary in any chronic regimen using sublingual ISDN is not known.

From large, well-controlled studies of other nitrates, it is reasonable to believe that the maximal

achievable daily duration of anti-anginal effect from ISDN is about 12 hours. No dosing regimen for ISDN has, however, ever actually been shown to achieve this duration of effect. In the absence of data from multiple-dose trials, and considering the capacity of organic nitrates to induce tolerance, it is not reasonable to assume that multiple sublingual ISDN tablets taken during the course of a day will all have similar effects.

INDICATIONS AND USAGE

Isosorbide dinitrate sublingual tablets are indicated for the prevention and treatment of angina pectoris due to coronary artery disease. However, because the onset of action of sublingual ISDN is significantly slower than that of sublingual nitroglycerin, sublingual ISDN is not the drug of first choice for abortion of an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. The isosorbide dinitrate sublingual tablet is contraindicated in patients who are allergic to ISDN or any of its other ingredients.

WARNINGS

Amplification of the vasodilatory effects of isosorbide dinitrate by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The benefits of sublingual ISDN in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use ISDN in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of ISDN. 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 ISDN may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to ISDN 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 sublingual ISDN 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.

Information for Patients

Patients should be told that the anti-anginal efficacy of ISDN is strongly related to its dosing regimen, so the prescribed schedule of dosing should be followed carefully. In particular, daily headaches sometimes accompany treatment with ISDN. 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 ISDN, since loss of headache may be associated with simultaneous loss of anti-anginal efficacy. Aspirin and/or acetaminophen, on the other hand, often successfully relieve ISDN-induced headaches with no deleterious effect on ISDN'S anti-anginal efficacy.

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

Drug Interactions

The vasodilating effects of ISDN may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Carcinogenesis. Mutagenesis. Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ISDN. In a modified two-litter reproduction study, there was no remarkable gross pathology and no altered fertility or gestation among rats fed ISDN at 25 or 100 mg/kg/day.

Pregnancy Category C

At oral doses 35 and 150 times the maximum recommended human daily dose. ISDN 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.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of sublingual ISDN 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.

ADVERSE REACTIONS

Adverse reactions to ISDN are generally dose-related, and almost all of these reactions are the result of ISDN's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur.

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 **OVERDOSAGE**).

Data are not available to allow estimation of the frequency of adverse reactions during treatment of isosorbide dinitrate sublingual tablets.

OVERDOSAGE

Hemodynamic Effects

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

There are no data suggesting what dose of ISDN 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 ISDN 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 ISDN is known, and no intervention has been subject to controlled studies as a therapy for ISDN overdose. Because the hypotension associated with ISDN 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 ISDN overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Nitrate ions liberated during metabolism of ISDN can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however and even assuming that the nitrate moieties of ISDN are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of ISDN 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 ISDN. 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 ISDN per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected

in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

As noted under **CLINICAL PHARMACOLOGY**, multiple studies with ISDN and other nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. Every dosing regimen for ISDN must provide a daily dose-free interval to minimize the development of this tolerance. In the case of sublingual tablets, it is probably true that one of the daily dose-free intervals must be somewhat longer than 14 hours.

As also noted under **CLINICAL PHARMACOLOGY**, the efficacy of daily doses after the first has never been demonstrated.

Large controlled studies with other nitrates suggest that no dosing regimen with Isosorbide Dinitrate Sublingual Tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

A patient anticipating activity likely to cause angina should take one isosorbide dinitrate sublingual tablet (2.5 to 5 mg) about 15 minutes before the activity is expected to begin. Isosorbide dinitrate sublingual tablets may be used to abort an acute anginal episode, but its use is recommended only in patients who fail to respond to sublingual nitroglycerin.

HOW SUPPLIED

Isosorbide Dinitrate Sublingual Tablets USP 2.5 mg: Yellow, round, compressed tablet imprinted "W1".

- Bottles of 100 tablets.
- Bottles of 1000 tablets.
- Unit Dose Boxes of 100 tablets.

Isosorbide Dinitrate Sublingual Tablets USP 5 mg: White, round, compressed tablet engraved with "W3".

- Bottles of 100 tablets.
- Bottles of 1000 tablets.
- Unit Dose Boxes of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

Also available: Isosorbide Dinitrate Oral Tablets in the following dosage strengths:

5 mg; in bottles of 100, 500, 1000 or unit dose boxes of 100 tablets.
10 mg; in bottles of 100, 500, 1000 or unit dose boxes of 100 tablets.
20 mg; in bottles of 100, 1000 or unit dose boxes of 100 tablets.

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724
Revised November 2007

PRINCIPAL DISPLAY PANEL

Isosorbide Dinitrate Sublingual Tablets, USP
NDC 0143-1765-01
2.5 mg/100 Tablets

PRINCIPAL DISPLAY PANEL

Isosorbide Dinitrate Subligual Tablets, USP
NDC 0143-1767-01
5 mg/100 Tablets

ISOSORBIDE DINITRATE

isosorbide dinitrate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-1765
Route of Administration	SUBLINGUAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ISOSORBIDE DINITRATE (UNII: IA7306519N) (ISOSORBIDE DINITRATE - UNII:IA7306519N)	ISOSORBIDE DINITRATE	2.5 mg

Inactive Ingredients

Ingredient Name	Strength
AMMONIUM PHOSPHATE, DIBASIC (UNII: 10LGE70FSU)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	W1
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-1765-01	100 in 1 BOTTLE		
2	NDC:0143-1765-10	1000 in 1 BOTTLE		
3	NDC:0143-1765-25	100 in 1 BOX, UNIT-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA086054	12/01/1978	

ISOSORBIDE DINITRATE

isosorbide dinitrate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-1767
Route of Administration	SUBLINGUAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOSORBIDE DINITRATE (UNII: IA7306519N) (ISOSORBIDE DINITRATE - UNII:IA7306519N)	ISOSORBIDE DINITRATE	5 mg

Inactive Ingredients

Ingredient Name	Strength
AMMONIUM PHOSPHATE, DIBASIC (UNII: 10LGE70FSU)	

ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	W3
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-1767-01	100 in 1 BOTTLE		
2	NDC:0143-1767-10	1000 in 1 BOTTLE		
3	NDC:0143-1767-25	100 in 1 BOX, UNIT-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA086055	12/01/1978	

Labeler - West-ward Pharmaceutical Corp (001230762)

Establishment

Name	Address	ID/FEI	Business Operations
West-ward Pharmaceutical Corp		001230762	MANUFACTURE(0143-1765, 0143-1767)

Revised: 5/2012 West-ward Pharmaceutical Corp