

## NITRATES (Systemic)

### VA CLASSIFICATION (Primary/Secondary)

Isosorbide dinitrate<sup>3</sup>/<sub>4</sub>CV250/CV900

Isosorbide mononitrate<sup>3</sup>/<sub>4</sub>CV250

Nitroglycerin<sup>3</sup>/<sub>4</sub>CV250/; CV900

Commonly used brand name(s): Apo-ISDN1; Cedocard-SR1; Coradur1; Coronex1; Deponit3; Dilatrate-SR1; IMDUR2; ISDN1; ISMO2; Isordil1; Isordil Tembids1; Isordil Titradoso1; Minitran3; Monoket2; Nitro-Bid3; Nitro-Bid IV3; Nitro-Dur3; Nitro-par3; Nitro-time3; Nitrocot3; Nitrodisc3; Nitrogard3; Nitroglyn E-R3; Nitroject3; Nitrol3; Nitrolingual3; Nitrong SR3; Nitrostat3; Sorbitrate1; Transderm-Nitro3; Tridil3. Another commonly used name is: Glyceryl trinitrate Nitroglycerin.

### Indications

#### Accepted

Angina pectoris, acute (treatment)<sup>3</sup>/<sub>4</sub>The sublingual, lingual, and extended-release buccal \* dosage forms of nitroglycerin and the sublingual \* and chewable dosage forms of isosorbide dinitrate are indicated for the relief of pain of an acute episode of angina pectoris due to coronary artery disease. Sublingual or lingual nitroglycerin is preferred; isosorbide dinitrate should be used in patients intolerant of or unresponsive to nitroglycerin. Sublingual isosorbide dinitrate \* or sublingual or lingual nitroglycerin may be administered to relieve acute anginal attacks that may occur while the patient is on oral prophylactic therapy.

Angina pectoris, acute (prophylaxis)<sup>3</sup>/<sub>4</sub>The sublingual, lingual \* , and extended-release buccal dosage forms of nitroglycerin and the sublingual or chewable dosage forms of isosorbide dinitrate are indicated for prophylaxis of acute angina attacks in situations (such as stress or exertion) likely to provoke such attacks.

Angina pectoris, chronic (treatment)<sup>3</sup>/<sub>4</sub>The regular, chewable, sublingual, and extended-release oral dosage forms of isosorbide dinitrate; the regular and extended-release oral dosage forms of isosorbide mononitrate; and the extended-release oral and buccal dosage forms of nitroglycerin are indicated for the prophylaxis and long-term treatment of angina pectoris due to coronary artery disease, but not in the treatment of acute anginal attacks (except for chewable isosorbide dinitrate and buccal nitroglycerin). Rapid first-pass hepatic destruction of nitroglycerin may increase the dosage requirements 9 of the oral extended-release capsules and tablets in the prophylaxis and treatment of angina.

Nitroglycerin injection is indicated in the treatment of unstable angina pectoris in patients who have not responded to recommended doses of other organic nitrates and/or a beta-blocker.

Nitroglycerin ointment and nitroglycerin transdermal systems are indicated for the prophylaxis and long-term treatment of angina pectoris but are not indicated for the relief of an acute angina episode.

#### Hypertension (treatment) or

Hypotension, controlled<sup>3</sup>/<sub>4</sub>Nitroglycerin injection is indicated for blood pressure control during certain surgical procedures and for controlled hypotension during surgery to reduce bleeding into the surgical field.

Myocardial infarction (treatment adjunct) or

Congestive heart failure (treatment) Nitroglycerin injection is indicated in the adjunctive therapy for congestive heart failure associated or not associated with acute myocardial infarction. (Treatment of congestive heart failure not associated with acute myocardial infarction is not included in Canadian product labeling.) [ Sublingual] \* , [ lingual] \* , and [ topical] \* nitroglycerin and; [ regular oral] \* , [chewable] , and [sublingual] \* isosorbide dinitrate are also being used for treatment of congestive heart failure, whether or not it is associated with acute myocardial infarction. In general, the oral extended-release dosage forms are not recommended because the effects are difficult to terminate if excessive hypotension or tachycardia develops, although these dosage forms may be acceptable once the patient is stabilized 9.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one nitrate may be sensitive to other nitrates also, although the reaction is rare. Patients sensitive to nitrites may be sensitive to nitrates also, although the reaction is rare.

Carcinogenicity

Studies with isosorbide dinitrate or nitroglycerin have not been done 15, 16, 17, 18, 19, 22.

Studies in mice given oral isosorbide mononitrate at doses of up to 900 mg per kg of body weight (mg/kg) per day (102 times the human exposure comparing body surface area) did not reveal evidence of carcinogenicity. 50

Pregnancy/Reproduction

Fertility Isosorbide dinitrate: Studies in rats given isosorbide dinitrate at doses of 25 or 100 mg/kg per day found no impairment of fertility 15, 16, 17, 18, 19.

Isosorbide mononitrate: No adverse effect on fertility was observed in male and female rats given isosorbide mononitrate at doses of up to 500 mg/kg per day (125 times the human exposure comparing body surface area). 50

Pregnancy Adequate and well-controlled studies in humans have not been done.

Studies in rabbits given isosorbide dinitrate in oral doses of 35 and 150 times the maximum daily recommended human dose have shown a dose-related increase in embryotoxicity. Administration of isosorbide mononitrate to rats at doses of 500 mg/kg per day (125 times the human exposure comparing body surface area) was associated with increased rates of prolonged gestation, prolonged parturition, stillbirths and neonatal death, and decreases in birth weight, live litter size, and pup survival. 50 No evidence of developmental abnormalities, fetal abnormalities, or other effects on reproductive performance was observed in rats and rabbits given isosorbide mononitrate at doses of 250 mg/kg per day. 50

FDA Pregnancy Category C.

### Breast-feeding

It is not known whether nitrates are distributed into breast milk. However, problems in humans have not been documented.

### Pediatrics

Appropriate studies on the relationship of age to the effects of nitrates have not been performed in the pediatric population.

### Geriatrics

Appropriate studies on the relationship of age to the effects of nitrates have not been performed in the geriatric population. However, elderly patients may be more sensitive to the hypotensive effects of nitrates. In addition, elderly patients are more likely to have age-related renal function impairment, which may require caution in patients receiving nitrates.

### Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate) not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Acetylcholine or