

Vasodilators Coronary Summary

FDA-APPROVED INDICATIONS AND DOSAGES

Drug	Manufacturer	Indication(s)	Dosage	Availability
isosorbide dinitrate (Isordil®) ¹	generic, Valeant	Prevention of angina pectoris due to coronary artery disease	Immediate-release <ul style="list-style-type: none"> Initial: Take 5 to 20 mg two to three times daily Maintenance: 10 to 60 mg two to three times daily; Do not exceed 480 mg/day 	Tablets: <ul style="list-style-type: none"> 5, 10, 20, 30, 40 mg Isordil tablets: <ul style="list-style-type: none"> 40 mg Isordil Titradosse tablets: <ul style="list-style-type: none"> 5 mg
isosorbide dinitrate ER (IsoDitratre ER®, Dilatrate-SR®) ^{2,3}	generic, Amedra, Actient	Prevention of angina pectoris due to coronary artery disease	Extended-release <ul style="list-style-type: none"> Take 40 mg by mouth twice daily; at least 18 hours apart. Do not exceed 160 mg/day 	Extended-release tablets: <ul style="list-style-type: none"> 40 mg Extended-release capsules: <ul style="list-style-type: none"> 40 mg
isosorbide dinitrate sublingual ⁴	generic	<ul style="list-style-type: none"> *Treatment of acute episodes of angina Prevention of effort-induced or stress-induced angina 	<ul style="list-style-type: none"> Acute relief: Take 2.5 to 10 mg SL every two to three hours as needed Prophylaxis: Take 2.5 to 5 mg SL about 15 minutes prior to the expected activity 	Sublingual tablets: <ul style="list-style-type: none"> 2.5, 5 mg
isosorbide mononitrate ⁵	generic	Prevention of angina pectoris due to coronary artery disease	20 mg twice daily, with doses given seven hours apart; 5 mg may be given to patients with small stature; Do not exceed 40 mg/day	Tablets: <ul style="list-style-type: none"> 10, 20 mg
isosorbide mononitrate ER (Imdur®) ⁶	generic, Merck Sharp & Dohme	Prevention of angina pectoris due to coronary artery disease	Initial <ul style="list-style-type: none"> 30 to 60 mg once daily, preferably in the morning upon awakening; increased to 120 mg; Do not exceed 240 mg/day 	Extended-release tablets: <ul style="list-style-type: none"> 30, 60, 120 mg

FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)	Dosage	Availability
nitroglycerin ER ⁷	generic	Prevention of angina pectoris due to coronary artery disease	Take 2.5 to 6.5 mg three to four times daily; titrate to clinical response and adverse reactions as needed	Extended-release capsules: 2.5, 6.5, 9 mg
nitroglycerin lingual (NitroMist [®] , Nitrostat [®]) ^{8,9}	generic, Akrimax, Pfizer	<ul style="list-style-type: none"> Acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease 	<p>Acute relief:</p> <ul style="list-style-type: none"> Translingual spray: One to two sprays on or under the tongue, may repeat as needed every five minutes up to three sprays in 15 minutes Sublingual tablets: One tablet dissolved under the tongue or in the buccal pouch immediately following indication of anginal attack, may repeat every five minutes up to three doses in 15 minutes <p>Prophylaxis of angina pectoris:</p> <ul style="list-style-type: none"> Use five to 10 minutes prior to engaging in activities that might precipitate an acute attack 	<p>Translingual aerosol spray:</p> <ul style="list-style-type: none"> 400mcg/spray 8.5 gram (230 doses), 4.1 gram (90 doses) <p>Sublingual tablets:</p> <ul style="list-style-type: none"> 0.3, 0.4, 0.6 mg
nitroglycerin ointment (Nitro-Bid [®]) ¹⁰	, Savage	Prevention of angina pectoris due to coronary artery disease	Apply 7.5 mg (1/2 inch) to 30 mg (2 inches) twice a day, onto 36 square inches of hairless area of skin (chest, abdomen, thighs); applied on rising in the morning and six hours later. The dose may be doubled, and even doubled again, if tolerance occurs.	<p>Nitro-Bid 2% topical ointment:</p> <ul style="list-style-type: none"> 30 gram, 60 gram 48 x 1 gram unit dose packets
nitroglycerin transdermal (Minitran [®] , Nitro-Dur [®]) ^{11,12}	generic, Medicus, Merck Sharp & Dohme	Prevention of angina pectoris due to coronary artery disease	Apply one patch topically every 24 hours; leave the patch on for 12 to 14 hours, then remove for 10 to 12 hours prior to applying the next patch.	Patch: 0.1, 0.2, 0.3, 0.4, 0.6, 0.8 mg/hr

* Nitroglycerin lingual (SL tablets, spray) is first-line therapy for the treatment for episode of acute angina; isosorbide dinitrate sublingual therapy is recommended in patients who fail to respond to SL nitroglycerin.¹³

Hydralazine/isosorbide dinitrate (Bidil[®]), which is not included in this summary, is indicated as adjunct therapy to standard therapy in self-identified African-American patients with heart failure.¹⁴

OVERVIEW^{15,16,17,18,19,20,21,22,23}

Angina pectoris (AP) is a clinical syndrome of coronary artery disease. It is caused by decreased oxygen delivery to myocardial tissue. It presents as chest discomfort, including burning, heaviness, or a sensation of choking, or pain in the jaw, neck, ear, and shoulder. Symptoms may also include nausea, shortness of breath, or sweating. It is associated with an increased risk of cardiac death and myocardial infarction.

Nitrates (nitroglycerin and isosorbide) approved to treat or prevent AP, caused by coronary artery disease, include immediate- and extended-release oral tablets, translingual spray and sublingual tablet, and transdermal ointment and patches. Lingual formulations of nitroglycerin and isosorbide dinitrate are used to relieve the symptoms of an acute attack, nitroglycerin being first-line therapy. Nitroglycerin sublingual can also be taken prior to engaging in activities that may precipitate an acute attack.

Nitrates (nitroglycerin and isosorbide) relax vascular smooth muscle causing venous and arterial dilation. This vasodilation leads to pooling of venous blood and decreased venous return to the heart (preload), reduction in systemic and pulmonary arterial pressure (after load), and reduced cardiac output. By decreasing preload and after load, myocardial tissue oxygen demand is reduced and pain of angina pectoris is improved.

Nitroglycerin is poorly absorbed in the gastrointestinal tract; however, it has good absorption via transmucosal and transdermal routes. In general, nitroglycerin has a faster onset and shorter duration of action compared to isosorbide formulations. Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate. Unlike the dinitrate, it is nearly completely bioavailable and has no active metabolites.

SPECIAL USAGE CONSIDERATIONS^{24,25,26,27,28,29,30,31}

Nitrates are contraindicated in patients with increased intracranial pressure, severe anemia, closed-angle glaucoma, and in those who have known nitrate hypersensitivity. Isosorbide dinitrate should be used with caution in patients with pre-existing hypotension, particularly orthostatic hypotension, or in patients with hypovolemia/dehydration. Nitrates are contraindicated in patients taking phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil, tadalafil, vardenafil). Nitrates should be used cautiously in patients with recent myocardial infarction because drug-induced hypotension and/or tachycardia can worsen or expand ischemic damage.

Headache, flushing, and hypotension are common side effects with these products, due to their vasodilatory actions.

Extended-release nitrate products should be avoided in patients with gastrointestinal conditions, such as hypermotility or malabsorption syndromes, since this dosage form may not dissolve and may be excreted intact.

Nitroglycerin lingual spray (NitroMist) should be administered on or under the tongue, closing the mouth immediately afterward. Do not swallow immediately after the dose of translingual spray is administered. Do not spit or rinse mouth for five to 10 minutes following administration. Do not crush or chew extended-release tablets or capsules. Administer extended-release formulations with a full

glass of water. Administer sublingual tablets while patient is in a seated position. Do not swallow, crush, or chew sublingual tablets.

Nitroglycerin ointment, as well as nitroglycerin and isosorbide dinitrate/mononitrate controlled-release capsules or tablets, should not be used to abort an acute anginal episode due to the relative slow onset of action.

Nitroglycerin ointment (Nitro-Bid) should be applied to the truncal area, on a hairless area of skin, using the application papers; avoid contact with hands. Allergic reactions are uncommon, although contact dermatitis or fixed drug eruptions have been reported.

Nitroglycerin transdermal patch (Minitran, Nitro-Dur) should be applied to a hairless area of skin. If patch becomes loose, replace with another patch. Do not cut patch. Remove patch prior to cardioversion or magnetic resonance imaging (MRI) scan.

Tolerance is likely to develop with the use of nitrate products. A 12 hour nitrate-free period is recommended for transdermal and transmucosal formulations.³² Although the interdosing interval sufficient to avoid tolerance to isosorbide dinitrate remains unknown, a nitrate-free interval greater than 18 hours is recommended. For immediate-release isosorbide dinitrate an interdosing interval of 14 hours is recommended. A nitrate-free interval of 10 to 12 hours has been recommended for nitroglycerin products. For immediate-release isosorbide mononitrate, a twice daily dosage regimen with the two doses given seven hours apart has been shown to avoid development of tolerance.

All products in this review are Pregnancy Category C. Safety and effectiveness of nitrates in pediatric patients has not been established. Elderly patients may be more sensitive to the hypotensive and bradycardic effects of nitrates, and should therefore be started on the lower end of the dose range and monitored carefully. Use nitrates with caution in patients with hepatic impairment.

Avoid abrupt discontinuation of nitrates following long-term or high-dose administration, to avoid potential for rebound angina.

Concomitant use of nitrates with other antihypertensive agents, peripheral vasodilators, beta-blockers, opiate agonists, phenothiazines, phosphodiesterase-5 (PDE-5) inhibitors, or moderate or excessive amounts of ethanol can cause additive hypotensive effects. Concomitant use of nitrates with sympathomimetics can result in increases in heart rate and blood pressure. Caution should be used with concurrent use of nitrates with rosiglitazone or alfuzosin.

PLACE IN THERAPY

Unstable angina is a clinical presentation of coronary artery disease. Coronary heart disease is the most common type of heart disease the leading cause of death in the United States.³³ Early diagnosis and management of this condition is essential to rule out myocardial infarction and prevent cardiac death. Sublingual nitroglycerin tablets or translingual spray are drugs of choice to abort acute anginal attacks and prophylactically to prevent angina due to activity.^{34,35} Due to intermittent administration, tolerance is not an issue with sublingual nitroglycerin. Translingual nitroglycerin spray offers convenience, due to product stability and ease of use. Treatment with translingual nitroglycerin spray resulted in a shorter time to resolution of chest pain than sublingual nitroglycerin tablets in 10 patients during a controlled trial.³⁶ All patients should be prescribed sublingual nitroglycerin tablets or nitroglycerin spray for immediate relief of angina.³⁷ Although nitroglycerin ointment has shown effectiveness in the prophylaxis of angina on exertion, variances in its absorption properties prevent

consistent accurate dosing, compared to the consistency of transdermal nitroglycerin patches.³⁸ Isosorbide dinitrate is recommended for intermittent nitrate therapy to prevent angina attacks. Large doses of sustained-release isosorbide dinitrate, given once daily, have been advocated to prevent tolerance from developing. Isosorbide mononitrate is dosed less frequently than the dinitrate formulations, with availability of a once daily extended-release tablet.

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