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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

NitroMist® is contraindicated in patients with severe anemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

2.2 Priming the Container

3 DOSAGE FORMS AND STRENGTHS

Lingual aerosol: 400 mcg per spray is available in either 230 metered sprays or 90 metered sprays per container.

4 CONTRAINDICATIONS

4.1 PDE5 Inhibitor Use

Administration of NitroMist® is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), as PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates.

4.2 Severe Anemia

NitroMist® is contraindicated in patients with severe anemia.

4.3 Increased Intracranial Pressure

NitroMist® is contraindicated in patients with increased intracranial pressure.

4.4 Hypersensitivity

NitroMist® is contraindicated in patients who have shown hypersensitivity to it or to other nitrates or nitrates. Skin reactions consistent with hypersensitivity have been observed with organic nitrates.

5 WARNINGS AND PRECAUTIONS

5.1 Tolerance

Excessive use may lead to the development of tolerance. The smallest number of doses required for effective relief of the acute angina attack should be used [see DOSAGE AND ADMINISTRATION (2)].

5.2 Hypotension

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

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

5.3 Hypertrophic Cardiomyopathy

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

5.4 Headache

Nitroglycerin produces dose-related headaches, which may be severe, Tolerance to headaches occurs.

6 ADVERSE REACTIONS

6.1 Headache, which may be severe and persistent, may occur immediately after nitroglycerin use.

6.2 Flushing, drug rash and exfoliative dermatitis have been reported in patients receiving nitrate therapy.

6.3 Prolonged hypotension, as manifest by vertigo, weakness, palpitation, and other symptoms, may develop occasionally, particularly in erect, immobile patients. Marked sensitivity to the hypotensive effects of nitrates (manifested by nausea, vomiting, weakness, diaphoresis, pallor, and collapse) may occur at therapeutic doses.

6.4 Syncope due to nitrate vasodilatation has been reported.

7 DRUG INTERACTIONS

7.1 PDE5 Inhibitors

Administration of NitroMist® is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), as PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates.

The time course and dose dependence of this interaction have not been studied, and use within a few days of one another cannot be recommended. Appropriate supportive care for the severe hypotension 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 use of any form of nitrates during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

7.2 Antihypertensives

Patients receiving antihypertensive drugs, beta-adrenergic blockers, and nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly.

Labeltol blocks the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effects. If labeltol is used with nitroglycerin in patients with angina pectoris, additional hypotensive effects may occur.
7.3 Aspirin
Consistent with aspirin and nitroglycerin has been reported to result in increased nitroglycerin maximum concentrations by as much as 67% and AUC by 78% when administered as a single dose. The vasodilatory and hemodynamic effects of nitroglycerin may be enhanced by concomitant administration of aspirin.

7.4 Race- and Type- Specific Pharmacokinetic Variability (R-PF)
Intrastravenous administration of nitroglycerin decreases the thrombolytic effect of tissue-type plasminogen activator (t-PA). Plasma levels of t-PA are reduced when coadministered with nitroglycerin. Therefore, caution should be observed in patients receiving nitroglycerin during t-PA therapy.

7.5 Hepatitis
Intrastravenous nitroglycerin reduces the anticoagulant effect of hepatic. Activated partial thromboplastin times (aPTT) should be monitored in patients receiving hepatic and intrastravenous nitroglycerin. This is not if it has an effect occurs following single nitroglycerin doses.

7.6 Ergotamine
Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability. Ergotamine is known to precipitate angina pectoris. Therefore, patients receiving ergotamine orally should avoid ergotamine and related drugs or be monitored for symptoms of ergotism if this is not possible.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy category C: Animal reproduction and teratogenicity studies have not been conducted with NitroMist or nitroglycerin sublingual tablets. It is also not known whether NitroMist can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. A teratology study was conducted in the third mating of F2 generation female rats administered dietary nitroglycerin for gestation day 6 to day 15 at doses levels used in the 3-generation reproduction study. In offspring of the high-dose nitroglycerin group, increased incidences of infant mortality were found, indicating probably reflects delayed development rather than a potential teratogenic effect, thus indicating no clear evidence of teratogenicity of nitroglycerin.

There are no adequate and well controlled studies in pregnant women. NitroMist should be given to a pregnant woman only if clearly needed.

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

8.4 Pediatric Use
The safety and effectiveness of nitroglycerin in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of NitroMist 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 elderly (greater than or equal to 65 years) and younger (less than 65 years) patients.

In general, geriatric patients, especially those with left ventricular failure, 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.

10 OVERDOSAGE
Signs and symptoms of hemodynamic effects: The effects of nitroglycerin overdose are generally the results of nitroglycerin’s capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protein manifestations, including increased intracranial pressure with any or all of the following: headache, neck stiffness, and vomiting; focal or generalized convulsion; laryngeal spasm; disturbances of consciousness; and more rarely, convulsions. No specific antidote to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotensive associated with nitroglycerin overdose is the result of vasodilatation and arterial pooling, prudent therapy in such situations should be directed toward increase in central fluid volume. Passive elevation of the patient’s legs may be insufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasopressors in this setting is not recommended.

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

11.2 Mechanism of Action
Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2-propanediol trinitrate (C3H3N3O9). The compound has a molecular weight of 227.9.

11.2.1 Pharmacodynamics
Nitroglycerin forms free radical nitric oxide (NO) that activates guanylate cyclase, resulting in an increase of guanosine 3',5'-monophosphate (cGMP) in smooth muscle and other tissues. This eventually leads to depolarization of myosin light chains, which regulates the contractile state in smooth muscle and results in vasodilatation.

11.2.2 Pharmacokinetics
The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle. Although venous effects predominate, nitroglycerin produces a dose-related decrease in both arterial and venous beds. Dilatation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood, decreases venous return to the heart, and reduces left ventricular end-diastolic pressure (preload). Nitroglycerin also reduces arterial blood pressure (systolic, diastolic, and mean), decreasing peripheral vascular resistance and arterial pressure (afterload), and dilates large epicardial coronary arteries; however, the extent to which this latter effect contributes to the relief of anginal pain is unclear.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, and pulmonary and systemic vascular resistances are also reduced. The heart rate is usually slightly increased, probably a reflex response to the fall in blood pressure, Cardiac index may be increased, decreased, or unchanged. Myocardial oxygen consumption or demand (as measured by the pressure-rate index, tension-time index, and stroke-work index) is decreased and a more favorable supply-demand ratio can be achieved. Patients with elevated left ventricular filling pressure and increased systemic vascular resistance in association with a depressed cardiac index are likely to experience an improvement in cardiac index. In contrast, when filling pressure and cardiac index are normal, cardiac index may be slightly reduced following nitroglycerin administration.