

DATA SHEET

NITROLINGUAL PUMPSPRAY

Glyceryl trinitrate 0.4 mg/metered dose

Presentation

Metered dose (non-aerosol, CFC free) delivering 0.4 mg glyceryl trinitrate per spray emission.

Uses

Actions

Glyceryl trinitrate, an organic nitrate, is a vasodilator, which has effects on both arteries and veins.

The principal pharmacological action of glyceryl trinitrate is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilatation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).

The mechanism by which glyceryl trinitrate relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of glyceryl trinitrate and presumably, a more favourable supply-demand ratio is achieved. While the large epicardial coronary arteries are also dilated by glyceryl trinitrate, the extent to which this action contributes to relief of exertional angina is unclear.

Therapeutic doses of glyceryl trinitrate 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, pulmonary vascular resistance and systemic vascular resistance are also reduced by glyceryl trinitrate therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced.

Pharmacokinetics

When administered sublingually, glyceryl trinitrate is rapidly absorbed from the mucosa of the mouth and reaches the vascular system, bypassing the liver. Maximum plasma concentration is reached approximately 4 minutes after administration.

Glyceryl trinitrate is rapidly metabolised *in vivo*, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. Two active

major metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolised to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

The plasma half-life following sublingual administration is 2½ to 4½ minutes. Plasma protein binding is approximately 60 %. Glyceryl trinitrate is principally renally eliminated and less than 1 % is excreted unchanged.

Indications

Treatment of acute angina pectoris. As well as relieving the pain of an acute attack, Nitrolingual Spray may be used prophylactically five to ten minutes prior to engaging in activities which may precipitate an acute attack.

Dosage and Administration

At the onset of an attack, initially one spray (400 microgram) should be sprayed under the tongue, followed by a second spray if pain relief has not occurred within 5 minutes. No more than two metered doses are recommended. If chest pain persists, seek prompt attention.

During application the patient should rest in the sitting position. The bottle should be kept vertical with the nozzle head uppermost. Hold the opening in the nozzle head as close to the open mouth as possible. Close the mouth immediately after each dose.

There is no need to shake the canister. Spray under the tongue or onto the oral mucosa.

Patients should be instructed to familiarise themselves with the position of the spray opening for ease of use at night. The spray should not be inhaled.

Contraindications

- Known sensitivity to glyceryl trinitrate or idiosyncratic reaction to organic nitrates.
- Acute circulatory failure (shock, circulatory collapse).
- Uncorrected hypovolaemia.
- Pronounced hypotension (systolic blood pressure below 90 mmHg).
- Increased intracranial pressure (eg. head trauma or cerebral haemorrhage).
- Severe anaemia or arterial hypoxaemia (see Precautions).
- Constrictive pericarditis and pericardial tamponade.
- Cardiogenic shock.

Concomitant administration of certain medicines (phosphodiesterase inhibitors) for the treatment of erectile dysfunction and **NITROLINGUAL** is contraindicated due to an increase in the hypotensive effect of **NITROLINGUAL**. This may result in severe side effects such as syncope or myocardial infarction.

Warnings and Precautions

The use of any form of glyceryl trinitrate during the early days of acute myocardial infarction requires particular attention to haemodynamic monitoring and clinical status.

Because Nitrolingual Spray is more stable than glyceryl trinitrate tablets, it is possible that some patients transferred to the spray will receive a larger dose of the drug than usual. This may increase possible side effects, eg. headache (*see Adverse Reactions*).

General: Severe hypotension, particularly with upright posture, may occur even with small doses of glyceryl trinitrate. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood

pressure (eg. below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Tolerance: Tolerance to this drug and cross tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory.

Intermittent therapy, such as with Nitrolingual Spray, will reduce the likelihood of tolerance developing to glyceryl trinitrate.

Withdrawal: Various clinical trials in angina patients indicate that withdrawal of glyceryl trinitrate may cause rebound of haemodynamic effect and a more ready provocation of anginal attack.

Hypoxaemia: Arterial oxygen tension decreases after administration of glyceryl trinitrate in normal subjects and in patients with coronary artery disease.

Caution should be observed in patients with severe ischaemic heart disease as a decrease in available oxygen may oppose its antianginal effect.

Methaemoglobinaemia: Methaemoglobinaemia has been reported in association with high doses of glyceryl trinitrate therapy. This may be clinically significant, especially in the presence of methaemoglobin reductase deficiencies or in congenital methaemoglobin variants.

Use in Pregnancy: Category B2.

The safety of glyceryl trinitrate administered to women who are or who may become pregnant has not been established. Therefore, Nitrolingual Spray should not be given to pregnant women unless, in the judgment of the doctor, the expected benefit outweighs any potential risk.

Use in lactation: It is not known whether glyceryl trinitrate is excreted in human milk. Caution is advised when glyceryl trinitrate is administered to a breastfeeding mother.

Use in children: The safety and effectiveness of glyceryl trinitrate in children have not been established.

NITROLINGUAL is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Adverse Reactions

Generally dose related, particularly headache and hypotension. Headache, which may be severe and persistent, is the most commonly reported side effect. The following adverse events observed on occasion during treatment with organic nitrates but not necessarily Nitrolingual Spray are as follows.

More common reactions:

Nervous system. The most frequent adverse reaction in patients treated with glyceryl trinitrate is headache, which is dose dependent. The individual sensitivity to headache varies greatly. Dizziness and fainting, especially on standing, have also been reported.

Less common reactions:

Biochemical. Decreased arterial oxygen tension.

Cardiovascular. Tachycardia, bradycardia, hypotension, palpitations.

Dermatological. Cutaneous flushing, exfoliative dermatitis.

Gastrointestinal. Nausea and vomiting are both uncommon.

Haematological. Methaemoglobinaemia.

Musculoskeletal. Muscle twitching, weakness

Nervous system. Apprehension, restlessness.

Abrupt withdrawal may precipitate angina. Withdrawal may also exacerbate Raynaud's phenomenon in susceptible patients.

Interactions

Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Glyceryl trinitrate acts directly on vascular muscle. Therefore, any other agent that directly or indirectly acts on vascular smooth muscle can be expected to have decreased or increased effect depending upon the agent. Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Glyceryl trinitrate may potentiate the hypotensive and anticholinergic effects of tricyclic antidepressants.

Concomitant use of **NITROLINGUAL** and certain medicines (phosphodiesterase inhibitors) for the treatment of erectile dysfunction enhances the hypotensive effect. Therefore, the concomitant administration of **NITROLINGUAL** and these medicines is contraindicated. If a patient treated with these medicines for erectile dysfunction needs a rapidly effective nitrate (eg in the case of an acute angina pectoris attack) he/she must be hospitalised immediately.

Overdosage

Symptoms: Nitrate overdosage may result in severe hypotension, persistent throbbing headache, vertigo, palpitation, visual disturbance, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (possibly with colic and even bloody diarrhoea), syncope (especially in the upright posture), methaemoglobinaemia with cyanosis and anorexia, initial hyperpnoea, dyspnoea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma followed by clonic convulsions, and possibly death due to circulatory collapse.

Treatment: Keep the patient recumbent and comfortably warm. Hypotension and reflex tachycardia caused by overdosage can be treated by elevating the legs. Since the duration of the haemodynamic effects following overdosage with glyceryl trinitrate is quite short (because of its short half-life) additional measures are usually not required.

Administer oxygen and artificial ventilation if necessary.

In cases of severe overdose apply the general guidelines for treating overdose and/or shock therapy. For pronounced hypotension, volume expansion can be performed.

However, if further therapy is indicated, administration of an intravenous α -adrenergic agonist (eg. metaraminol) should be considered.

Warning: Adrenaline is ineffective in reversing the severe hypotensive events associated with overdose. It and related compounds are contraindicated in this situation.

Methaemoglobin: Case reports of clinically significant methaemoglobinaemia are rare at conventional doses of organic nitrates. The formation of methaemoglobin is dose related and in the case of genetic abnormalities of haemoglobin that favour methaemoglobin formation, even conventional doses of organic nitrates could produce harmful concentrations of methaemoglobin. If methaemoglobinaemia is present, administration of methylene blue (1% solution), 1 to 2 mg/kg bodyweight intravenously, may be required.

Pharmaceutical Precautions

Store at temperature below 30°C. The shelf-life of Nitrolingual Pump Spray is 3 years. Protect from frost, heat and sunlight. Do not puncture or break even when empty.

Medicine Classification

Pharmacist only medicine

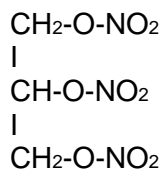
Package Quantities

Pumpspray containing either 75, 200 or 250 metered doses per bottle.

Further Information

CAS registry number: 55-63-0, molecular weight: 227.1, molecular formula: $C_3H_5(ONO_2)_3$.
Chemical Name: 1,2,3 - propanetriol trinitrate.

Chemical structure:



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