NEW ZEALAND DATA SHEET

1. GLYTRIN SPRAY

Glyceryl trinitrate 400 micrograms/metered dose

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glytrin spray 400 micrograms/metered dose: Metered dose (aerosol, CFC free) oromucosal (sublingual) spray solution delivering 400 micrograms glyceryl trinitrate per spray.

3. PHARMACEUTICAL FORM

Spray.

Excipients with known effect:

For the full list of excipients, see section 6.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of 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.

4.3 Contraindications

- Known sensitivity to glyceryl trinitrate or idiosyncratic reaction to organic nitrates.
- Known sensitivity to any excipients
- 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 medicines for male erectile dysfunction and GLYTRIN Spray is contraindicated due to an increase in the hypotensive effect of GLYTRIN Spray. This may result in severe side effects such as syncope or myocardial infarction.

4.4 Special warning and precautions for use

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 GLYTRIN 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 (e.g. 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 GLYTRIN 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 children: The safety and effectiveness of glyceryl trinitrate in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Therefore, Alcohol shall be avoided because of the hypotensive effect.

Vasodilators, antihypertensives, diuretics and neuroleptics can increase nitrate-induced hypotension.

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 GLYTRIN Spray and medicines for male erectile dysfunction enhances the hypotensive effect. Therefore, the concomitant administration of GLYTRIN Spray and medicines for male erectile dysfunction is contraindicated. If a patient treated with medicines for male erectile dysfunction needs a rapidly effective nitrate (e.g. in the case of an acute angina pectoris attack) he/she must be hospitalised immediately.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy:

Category B (23rd edition "Medicines in Pregnancy", Australia)

The safety of glyceryl trinitrate administered to women who are or who may become pregnant has not been established. Therefore, GLYTRIN 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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 GLYTRIN 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. Allergic skin reactions

Gastrointestinal: Nausea and vomiting are both uncommon; tongue oedema or swelling (as a symptom of hypersensitivity).

Haematological: Methaemoglobinaemia.

Musculoskeletal: Muscle twitching, weakness

Nervous system: Apprehension, restlessness, vertigo

Application Site Conditions: Burning sensation, stinging sensation, tongue blistering

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions.

https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 a-adrenergic agonist (e.g. 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 2mg/kg bodyweight intravenously, may be required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glyceryl trinitrate acts on vascular smooth muscles to produce arterial and venous vasodilation. The vasodilation results in a reduction of venous return and an improvement in myocardial perfusion with the result of a reduction in the work performed by the heart and hence reduced oxygen demand.

5.2 Pharmacokinetic properties

Glyceryl trinitrate is rapidly absorbed through the buccal and sublingual mucosa, and in man peak concentrations in plasma are observed within four minutes of sublingual administration.

The absolute bioavailability after sublingual administration is approximately 39%. After sublingual administration the plasma levels have shown a wide range of intra and inter-individual variability.

The compound is extensively metabolised by liver enzymes and has a plasma half-life of 1-3 minutes. The principle mechanism of metabolism involves denitration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other excipient:

Ethanol (ethanol 96%), Norflurane (1,1,1,1-tetrafluroethane), peppermint oil.

The propellant is CFC free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from date of manufacture.

6.4 Special precautions for storage

Store at temperature below 25°C. Protect from frost, heat and sunlight. GLYTRIN Spray is a pressurised aluminium canister which must not be pierced or burnt even after use. Patients, especially those who smoke should be warned not to use GLYTRIN Spray near a naked flame.

6.5 Nature and contents of container

Metered dose spray containing 200 or 250 doses per aluminium container.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Pharmacist only medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

24 May 2001

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19 March 2018