NEW ZEALAND DATA SHEET

DBL™ GLYCERYL TRINITRATE FOR INJECTION

Name of Medicine
Glyceryl trinitrate

Presentation
DBL™ Glyceryl Trinitrate for Injection is available in ampoules in 50 mg glyceryl trinitrate/10 mL.

Uses
Glyceryl trinitrate relaxes smooth muscle, including vascular muscle and reduces blood pressure. Its anti-anginal effect is exerted by reducing myocardial oxygen demand through peripheral vasodilation. This causes decreased venous tone resulting in a reduction in preload and decreased arterial resistance resulting in a reduction in afterload.

Pharmacokinetics
Glyceryl trinitrate is rapidly metabolised after injection so that a constant infusion is required to maintain levels. Metabolism occurs by hydrolysis to dinitrates and the mononitrate. Extrahepatic clearance is high. A relationship between clinical effect and plasma concentration of glyceryl trinitrate has not been determined.

Indications
DBL™ Glyceryl trinitrate for Injection for intravenous infusion, are indicated as follows:

1. Acute myocardial infarction with or without left ventricular failure.
2. Left heart failure associated with subacute and acute pulmonary oedema.
3. To reduce ventricular ectopic activity following myocardial infarction.
4. To reverse symptomatic coronary artery spasm following provocative testing in the diagnosis of variant angina.
5. Control of hypertension during surgical cardiovascular procedures and in the production of controlled hypotension during such procedures.
6. Treatment of angina pectoris in patients who have not responded to recommended doses of organic nitrates and/or a beta blocker.

Dosage and Administration
Dosage is affected by the type of infusion set used (see below). Dosage recommendations represented as mcg glyceryl trinitrate per minute can only be offered as a starting infusion rate. The correct dose for individual patients will be determined by the response to therapy. All patients should be on continuous cardiovascular monitoring during infusion therapy.

The dosage for DBL™ Glyceryl Trinitrate for Injection infusion solution should be initially 5mcg/minute delivered through an infusion pump capable of exact and constant medicine delivery. Increments should be cautious and adjusted to the clinical situation. Initially titration should be in 5mcg/minute increments with increases each 3-5 minutes until some response is noted.

If there is no response at 20mcg/minute, larger increments may be used, but once a blood pressure response is observed the increment should be reduced in magnitude and with longer intervals.

There is no fixed dose of DBL™ Glyceryl Trinitrate for Injection. Each patient must be titrated to his/her individual needs. Continuous monitoring of physiological parameters must be performed to achieve the correct dose. Maintenance of adequate systemic B.P. and coronary perfusion is essential.

The maximum dose is 8 (-10) mg per hour of glyceryl trinitrate.

DBL™ Glyceryl Trinitrate for Injection must be diluted.
DBL™ Glyceryl Trinitrate for Injection is compatible with the following infusion solutions:
- 0.9% NaCl solution
- 5% Dextrose.

Contraindications
Glyceryl trinitrate may not be used if there is:
- Acute circulatory failure (shock, circulatory collapse).
- Pronounced hypotension (systolic blood pressure < 90mmHg).
- Cardiogenic shock, in so far as sufficiently high left ventricular end-diastolic pressure is not ensured by intra-aortal counterpulsation or positive inotropic medicines.
- Concomitant administration of a soluble guanylate cyclase (GC) stimulator, such as riociguat due to potentiation of hypotensive effects.

For acute myocardial infarction with low filling pressures, glyceryl trinitrate should only be used with caution. Administration of glyceryl trinitrate for acute myocardial infarction should only be performed under a doctor's supervision. A drop in systolic pressure below 90mmHg should be avoided.

Concomitant administration of sildenafil (Viagra) and DBL™ Glyceryl Trinitrate for Injection is contraindicated due to an increase in the hypotensive effect of DBL™ Glyceryl Trinitrate for Injection. This may result in severe side effects such as syncope or myocardial infarction.

Warnings and Precautions
Warning: Intravenous Giving Sets
- Glyceryl trinitrate is readily absorbed onto certain plastics. The dilution and storage of glyceryl trinitrate for i.v. infusion should only be in glass. Plastic parenteral solution containers should not be used.
- Some filters absorb glyceryl trinitrate. Filters in the i.v. giving set should be avoided.

Adsorption is substantially less (5% or less) where polyethylene or polypropylene sets are utilised. Highest adsorption rates occur when the flow rates are low, glyceryl trinitrate concentrations are high, and the tubing is long.

However, because the amount of vascular binding varies inter-individually there is no correlation between plasma level and the effect. Higher plasma levels can be measured in arterial than in venous blood. In patients showing a greater response to nitrates, lower plasma levels indicate a high vascular binding. Therefore, the dose is always chosen individually according to the prevailing haemodynamic parameters.

It is recommended that:
- That low adsorptive giving sets are utilised where possible.
- That dosage is individually titrated to patient needs by careful attention to dosage rates and response as documented by physiological monitoring.

In summary, the ideal giving set should be as short as possible, not include a blood filter or burette chamber and, if possible, be of different material than PVC.

Pregnancy and Lactation
Pregnancy Category: B2

Animal experiments have provided no evidence of damage to the foetus by glyceryl trinitrate. However, glyceryl trinitrate should only be administered under a doctor's supervision during pregnancy and lactation.

Diabetes
Special care is required when treating diabetic patients since the medicine contains 5% w/v glucose.

Adverse Effects
Headaches caused by vasodilation occur frequently, especially at the onset of therapy. Flushing, drowsiness, orthostatic hypotension and reflex tachycardia are reported occasionally. Less often states of collapse occur, sometimes accompanied by bradyarrhythmias. In rare cases where there is a large drop in blood pressure, symptoms of angina pectoris may be enhanced.
Interactions
Concurrent administration of other vasodilators, antihypertensive agents, calcium antagonists, tricyclic antidepressants and alcohol may enhance the antihypertensive effect of glyceryl trinitrate. When used concurrently with dihydroergotamine, glyceryl trinitrate may cause an increase in the DHE level and thus enhance its effect. Simultaneous administration of heparin and glyceryl trinitrate diminishes the effect of heparin.

Concomitant use of DBL™ Glyceryl Trinitrate for Injection and sildenafil (Viagra) enhances the hypotensive effect. Therefore, the concomitant administration of DBL™ Glyceryl Trinitrate for Injection and Viagra is contraindicated. If a patient treated with sildenafil (Viagra) needs a rapidly effective nitrate (e.g. in the case of an acute angina pectoris attack) he/she must be hospitalised immediately.

Overdosage
Glyceryl trinitrate is well tolerated and has a very wide safety margin. In the event of overdose a higher incidence of the known undesirable effects may occur, such as headaches, drop in blood pressure with orthostatic regulatory disorders and reflex tachycardia. At higher doses (> 20mcg/kg body weight) anticipate formation of methaemoglobin, cyanosis and tachypnoea resulting from nitrate ions formed during metabolism (degradation).

Emergency Procedure
Direct all therapeutic counter-measures towards raising the blood pressure. In less serious cases placing the patient in the supine position with the legs higher than the head will cause the symptoms to disappear.

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

In exceptional cases, use sympathomimetic agents.

Depending on the degree of severity, the following antidotes may be used:
1. Vitamin C: 1g p.o. or as sodium salt i.v.
2. Methylene blue: up to 5mL of a 1% methylene blue solution i.v.
3. Toluidine blue: initially 2-4mL/kg body weight strictly intravenously.
4. Oxygen therapy, haemodialysis, exchange transfusion.

Pharmaceutical Precautions
Special Precautions for Storage: Store below 25°C. Protect from light.

Medicine Classification
Prescription Medicine.

Package Quantities
DBL™ Glyceryl Trinitrate for Injection 10 mL ampoules are supplied in boxes each containing 5 x 10 mL ampoules.

Further Information
Glyceryl trinitrate is propane-1,2,3-triol trinitrate. It has a molecular formula and weight of C₃H₅H₃O₉ and 227.1 respectively.

Each millilitre of DBL™ Glyceryl Trinitrate for Injection contains 5 milligrams of glyceryl trinitrate, absolute ethanol and propylene glycol in Water for Injections.

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