

GLYPRESSIN INJECTION

Terlipressin acetate 1mg/5ml

Presentation

GLYPRESSIN Injection 1mg: powder and solvent for solution for injection:

Powder (vial): white, lyophilized powder. Solvent (ampoule): clear, colourless liquid. Each vial of powder contains 1mg terlipressin diacetate (equivalent to terlipressin free base 0.86mg). The concentration of the reconstituted solution is 0.2mg terlipressin diacetate/mL.

GLYPRESSIN 0.1mg/mL solution for injection:

Clear, colourless liquid. One ampoule of 8.5mL contains 0.85mg terlipressin (as diacetate) equivalent to 0.1mg terlipressin/mL. One ampoule contains 1mg terlipressin diacetate. For full list of excipients see **Further Information**.

Uses

Actions

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues), ATC code: H01B A04.

Terlipressin initially has an effect of its own, but is converted by enzymatic cleavage to lysine vasopressin. Doses of 1 and 2mg effectively reduce the portal venous pressure and produce marked vasoconstriction. The lowering of portal pressure and azygos blood flow is dependent on dose. The effect of the low dose is reduced after 3 hours, while haemodynamic data show that 2mg is more effective than 1mg as the higher dose produces a dependable effect throughout the period of treatment (4 hours).

Pharmacokinetics

The pharmacokinetics follows a two-compartment model. It has been found that the half-life is approximately 40 minutes, metabolic clearance is approximately 9mL/kg/min and the distribution volume is approximately 0.5 L/kg.

The desired concentration of lysine vasopressin in plasma is found initially after approximately 30 minutes and reaches a peak value of 60 to 120 minutes after administration of GLYPRESSIN. Because of 100% cross-reaction between terlipressin and lysine vasopressin, there is no specific RIA method for these substances.

Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of single- and repeat-dose toxicity, and genotoxicity. At dosages relevant to humans, the only effects observed in animals were those attributable to the pharmacological activity of terlipressin. No pharmacokinetic data are available from animals to compare with humans the plasma concentrations at which these effects occurred, but as the route of administration was intravenous, a substantial systemic exposure can be assumed for the animal studies.

An embryo-foetal study in rats demonstrated no adverse effects of terlipressin, but in rabbits abortions occurred, probably related to maternal toxicity, and there were ossification anomalies in a small number of foetuses and a single isolated case of cleft palate.

No carcinogenicity studies have been performed with terlipressin.

Indications

GLYPRESSIN is indicated for the treatment of bleeding oesophageal varices.

Dosage and Administration

Dosage

An intravenous injection of GLYPRESSIN 2mg every 4 hours by bolus injection. The treatment should continue until bleeding has been controlled for 24 consecutive hours or for a maximum period of 48 hours. After the initial injection, subsequent doses can be reduced to 1mg of GLYPRESSIN every 4 hours in patients with a body weight of less than 50kg or when necessitated by adverse effects.

GLYPRESSIN must only be administered intravenously.

Contraindications

- Pregnancy
- Septic shock
- Hypersensitivity to terlipressin or any other excipients of the product

Warnings and Precautions

Blood pressure, heart rate and fluid balance should be monitored during treatment. To avoid local necrosis at the injection site, the injection must be given intravenously. Caution should be exercised in treating patients with hypertension or recognised heart disease. In patients with septic shock with a low cardiac output terlipressin should not be used.

Children and the elderly

Particular caution should be exercised in the treatment of children and elderly patients, as experience is limited in these groups.

There is no data available regarding dosage recommendation in these special patient categories.

Use in pregnancy and lactation

Treatment with GLYPRESSIN during pregnancy is contraindicated. GLYPRESSIN has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. GLYPRESSIN may have harmful effects on pregnancy and on the foetus.

Spontaneous abortion and malformation have been shown in rabbits after treatment with GLYPRESSIN.

Information on transfer of GLYPRESSIN to breast milk is insufficient. GLYPRESSIN should not be used in breast feeding women.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed..

Adverse Effects

MedDRA System Organ Class Disorder	COMMON (10-1%)	UNCOMMON (1-0.1%)	RARE (0.1-0.01%)	Not known (Cannot be estimated from the available data)
Metabolism	-	Hyponatraemia if fluid not monitored	-	-
Nervous system	Headache	-	-	-
Cardiac	Bradycardia	Atrial Fibrillation Ventricular extracystoles Tachycardia Chest pain		Torsade de point Cardiac failure

		Myocardial Infarction Fluid overload with pulmonary oedema		
Vascular	Peripheral vasoconstriction Peripheral ischaemia Facial pallor Hypertension	Intestinal ischaemia Peripheral cyanosis Hot flushes		
Respiratory		Respiratory distress Respiratory failure	Dyspnoea	
Gastrointestinal	Transient abdominal cramps Transient diarrhoea	Transient nausea Transient vomiting		
Skin and subcutaneous				Skin necrosis
Pregnancy, puerperium and perinatal conditions				Uterine hypertonus Decreased uterine blood flow
General		Injection site necrosis		

Interactions

The hypotensive effect of non-selective beta-blockers on the portal vein is increased with terlipressin. Concomitant treatment with medicinal products with a known bradycardic effect (e.g. propofol, sufentanil) may lower the heart rate and cardiac output. These effects are due to reflexogenic inhibition of cardiac activity via the vagus nerve due to the elevated blood pressure.

Overdosage

The recommended dose (2mg/4 hour) should not be exceeded as the risk of severe circulatory adverse effects is dose-dependent.

Pharmaceutical Precautions

List of excipients

Powder: Mannitol (E421); Hydrochloric acid

Solvent: Sodium chloride; Hydrochloric acid; Water for injections

Solution: Sodium chloride, acetic acid, sodium acetate trihydrate, water for injections

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life

Powder:

3 years

Solution:

2 years

This product should be used immediately after reconstitution.

Special precautions for storage

Powder:

Store below 25°C in original package in order to protect from light. The reconstituted solution must be used immediately after reconstitution.

Solution:

Store in a refrigerator (2°C-8°C). The ampoules are stored in the outer carton in order to protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

Powder:

GLYPRESSIN lyophilized powder is provided in a 6ml glass vial with a rubber stopper and green/silver coloured snap cap.

The diluent is provided in a 5ml glass ampoule.

Powder and diluent are provided together.

Solution:

8.5mL solution in clear, colourless, glass ampoules (Type 1 glass). Pack size: 5 x 8.5mL.

Further Information

Instructions for use/handling

Powder and solvent:

Mix solvent with powder for injection via the rubber stopper in the vial. The clear reconstituted solution must be injected intravenously immediately after reconstitution.

Any unused drug or waste materials should be disposed of in accordance with local requirements.

Name and Address

Exclusive New Zealand distributors:

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Date of Preparation

11 February 2011

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