

1. NAME OF THE MEDICINAL PRODUCT

GLYPRESSIN® solution for injection, 1 mg/8.5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 8.5 ml solution contains 1 mg terlipressin acetate, corresponding to 0.85 mg terlipressin free base. The concentration of the solution is 0.1 mg terlipressin free base/ml.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bleeding oesophageal varices

Treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for liver transplant.

4.2. Posology and method of administration

Bleeding Oesophageal Varices (BOV)

Posology

Adults:

Initially an i.v. injection of 2 ampoules of GLYPRESSIN® solution for injection (2 mg terlipressin acetate, equivalent to 1.7 mg terlipressin) is given every 4 hours. The treatment should be maintained until bleeding has been controlled for 24 hours, but up to a maximum of 48 hours. After the initial dose, the dose can be adjusted to 1 ampoule of GLYPRESSIN® solution for injection (1 mg terlipressin acetate, equivalent to 0.85 mg terlipressin) i.v. every 4 hours in patients with body weight < 50 kg or if adverse effects occur.

Method of Administration

i.v. injection

Hepatorenal Syndrome (HRS)

Posology

1 ampoule of GLYPRESSIN® solution for injection (1 mg terlipressin acetate, equivalent to 0.85 mg terlipressin) every 6 to 12 hours by slow intravenous bolus injection for 7 to 14 days (administered in association with albumin 20% 100 mL IV twice daily for 7 to 14 days).

If serum creatinine (SCr) has not decreased by at least 30% from the baseline value after 3 days, the dose can be increased to a maximum of 2 ampoules of GLYPRESSIN® solution for injection (2 mg terlipressin acetate, equivalent to 1.7 mg terlipressin) every 6 hours.

It is however recommended that the dose not be increased in patients with severe pre-existing cardiovascular disease or in the presence of an ongoing significant adverse event e.g. pulmonary oedema, ischaemia. Treatment should be continued until about 2 days after the patient achieves HRS reversal (SCr less than or equal to 132.6 µmol/L), or be discontinued if the patient undergoes dialysis or liver transplant or if SCr remains at or above baseline after 7 days of treatment.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction. When the patient's symptoms resolve, GLYPRESSIN® may be re-commenced at a lower dose or at a less frequent dosing interval (e.g., every 8 – 12 hours). The lowest doses used in the clinical studies ranged from 1.7 to 2.55 mg terlipressin/day. The maximum dose studied (TAHRS Study*) was 1.7 mg terlipressin every 4 hours.

*The study of Martín-Llahí et al. (2008), also known as the TAHRS study, was a supportive open-label, comparative multicentre study in 46 patients who were randomised in a 1:1 ratio to receive either intravenous terlipressin (0.85 – 1.7 mg (as 1 to 2 mg terlipressin acetate) every 4 hours) plus 20%

albumin or 20% albumin alone, for a maximum of 15 days. The majority of patients had HRS type 1 (35/46) and the remainder, HRS type 2 (11/46).

Method of Administration

i.v. injection

4.3 Contraindications

Contraindicated in pregnancy.

Hypersensitivity to terlipressin or any other excipients of the product.

4.4 Special warnings and precautions for use

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 i.v.

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

This medicinal product contains 1.33 mmol (or 30.7 mg) of sodium per ampoule. To be taken into consideration in patients on a controlled sodium diet.

Cardiovascular Effects

Terlipressin should only be used with caution and under strict monitoring of the patients in the following cases:

- uncontrolled hypertension
- cerebral or peripheral vascular diseases
- cardiac arrhythmias
- coronary artery disease or previous myocardial infarction

Terlipressin should not be used in patients with unstable angina or recent acute myocardial infarction.

Torsade de pointes

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including "Torsade de pointes" have been reported (see section 4.8). In most cases, patients had predisposing factors such as basal prolongation of the QT interval, electrolyte abnormalities (hypokalaemia, hypomagnesaemia) or medications with concomitant effect on QT prolongation. Therefore, extreme caution should be exercised in the use of terlipressin in patients with a history of QT interval prolongation, electrolyte abnormalities, concomitant medications that can prolong the QT interval (see section 4.5).

Ischaemic Events

To avoid local necrosis the injection must be administered intravenously.

During post-marketing experience several cases of peripheral ischemia and necrosis unrelated to the injection site have been reported. Patients with peripheral venous hypertension or morbid obesity seem to have a greater tendency to this reaction. Therefore, extreme caution should be exercised when administering terlipressin in these patients.

Respiratory Effects

Terlipressin may cause smooth muscle constriction and should be used with caution and under strict monitoring in patients with severe asthma or chronic obstructive pulmonary disease (COPD).

Laboratory Monitoring

During treatment with terlipressin, serum creatinine should be monitored at least daily as terlipressin should be used with caution in patients with renal insufficiency. Fluid balance and electrolytes should be monitored carefully as hyponatraemia, hypokalaemia, hypomagnesaemia and other electrolyte disturbances have been reported.

4.5 Interaction with other medicinal products and other forms of 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.

Terlipressin can trigger “torsade de pointes” (see sections 4.4 and 4.8). Therefore, extreme caution should be exercised in the use of terlipressin in patients with concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that may cause hypokalaemia or hypomagnesaemia (e.g. some diuretics).

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with terlipressin during pregnancy is contraindicated (see section 4.3 and 5.3).

Terlipressin has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. Terlipressin may have harmful effects on pregnancy and foetus.

Spontaneous abortion and malformation has been shown in rabbits after treatment with Terlipressin.

Breastfeeding

It is not known whether terlipressin is excreted in human breast milk. The excretion of terlipressin in milk has not been studied in animals. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with terlipressin should be made taking into account the benefit of breast-feeding to the child and the benefit of terlipressin therapy to the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The reporting of safety data rely on published literature and post marketing surveillance.

Clinical Trials

Three studies assessed safety as primary outcome in totally 1341 patients.

Caletti 1991, a prospective, uncontrolled observational study, enrolled 1258 patients. 21% of the patients experienced a side-effect. The side-effects reported were consistent with the known pharmacological actions of terlipressin.

Bruha 2009, a randomised, double-blind study enrolled 25 patients that were randomised to either 5-day or 10-day treatment. Serum sodium and serum creatinine decreased in both arms during treatment, but rose again after discontinuation of treatment.

Solà 2010, a retrospective cohort study, included 58 patients. Over a 5 day treatment period 67% of the patients developed acute reduction in serum sodium. The hyponatraemia was found to develop rapidly after start of therapy, but was usually reversible with a median recovery time of 4 days after discontinuation of terlipressin.

The most commonly reported undesirable effects in clinical trials (frequency 1-10%) are paleness, increased blood pressure, abdominal pain, nausea, diarrhoea and headache.

The antidiuretic effect of GLYPRESSIN® may cause hyponatraemia unless the fluid balance is controlled.

MedDRA			
System Organ Class	COMMON (≥1/100 to <1/10)	UNCOMMON (≥1/1000 to <1/100)	RARE (≥1/10000 to <1/1000)
Metabolism and nutrition disorders		Hyponatraemia if fluid not monitored	
Nervous system disorders	Headache		
Cardiac disorders	Bradycardia	Atrial Fibrillation Ventricular Extracystoles Tachycardia Chest pain Myocardial Infarction Fluid overload with pulmonary oedema Torsade de pointes Cardiac failure	
Vascular disorders	Peripheral vasoconstriction Peripheral ischemia Facial pallor Hypertension	Intestinal ischaemia Peripheral cyanosis Hot flushes	
Respiratory, thoracic and mediastinal disorders		Respiratory distress Respiratory failure	Dyspnoea
Gastrointestinal disorders	Transient abdominal cramps Transient diarrhoea	Transient nausea Transient vomiting	
Skin and subcutaneous tissue disorders		Skin necrosis	
Pregnancy, puerperium and perinatal conditions		Uterine hypertonus Uterine ischemia	
General disorders and administration site disorders		Injection site necrosis	

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing use:

- Venticular fibrillation (frequency not known)

4.9 Overdose

The recommended dose (2 mg terlipressin acetate or 1.7 mg terlipressin /4 hours) should not be exceeded as the risk of severe circulatory adverse effects is dose-dependent.

Elevated blood pressure in patients with recognised hypertension can be controlled with 150 mcg clonidine i.v.

Bradycardia requiring treatment should be treated with atropine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues). ATC-code: H01BA04.

Terlipressin initially has an effect of its own, but is converted by enzymatic cleavage to lysine vasopressin. Doses of 1 and 2 mg terlipressin acetate 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 2 mg terlipressin acetate is more effective than 1 mg as the higher dose produces a dependable effect throughout the period of treatment (4 hours).

5.2 Pharmacokinetic properties

The pharmacokinetics follows a two-compartment model. It has been found that the half-life is approximately 40 min., metabolic clearance is approximately 9 ml/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 min. and reaches a peak value of 60 to 120 min. after administration of GLYPRESSIN®. Because of 100% cross-reaction between terlipressin and lysine vasopressin, there is no specific RIA method for these substances.

5.3 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-fetal 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 fetuses and a single isolated case of cleft palate.

No carcinogenicity studies have been performed with terlipressin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Acetic acid
Sodium acetate trihydrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

8.5 ml solution in clear colourless glass ampoules (Type I glass).

Pack size:
5 x 8.5 ml

6.6. Special precautions for disposal and other handling

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

7. MANUFACTURER

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