1. NAME OF THE MEDICINAL PRODUCT

GLYPRESSIN® solution for injection, 1 mg/8.5 ml

INN: Terlipressin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 8.5 ml solution contains 1 mg terlipressin acetate, corresponding to 0.85 mg terlipressin. The concentration of the solution is 0.12 mg terlipressin acetate/ml, corresponding to 0.1 mg terlipressin/ml.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of bleeding oesophageal varices

Treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for liver transplant (see sections 4.2 and 4.4 on the risks in special populations).

4.2 Posology and method of administration

Bleeding Oesophageal Varices (BOV)

Posology

Adults:

Initially an IV injection of 2 mg terlipressin acetate (1.7 mg terlipressin free base) 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 mg IV every 4 hours in patients with body weight < 50 kg or if adverse effects occur.

Type 1 Hepatorenal Syndrome (HRS)

Posology

Adults:

1 ampoule of GLYPRESSIN® solution for injection (1 mg terlipressin acetateequivalent 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).

As an alternative to bolus injection, terlipressin can be administered as a continuous IV infusion with a starting dose of 2 mg of terlipressin acetate/24 hours and increased to amaximum of 12 mg of terlipressin acetate/24 hours. If volume expansion is needed, Glypressin can be diluted before administration. See section 6.7. Administration of terlipressin as continuous IV infusion has been associated with lower rates of severe adverse events than with administration by IV bolus (see section 5.1).

Special populations
Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442 µmol/L (5.0 mg/dL), unless the benefit is judged to outweigh the risks (see section 4.4).

Hepatic impairment
Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥39, unless the benefit is judged to outweigh the risks (see section 4.4).

Elderly:
There is no data available regarding dosage recommendation in the elderly.

Paediatric population:
There is no data available regarding dosage recommendation in the paediatric population.

Method of Administration
IV injection
Type 1 hepatorenal syndrome: IV injection or IV infusion

4.3 Contraindications
Contraindicated in pregnancy.
Hypersensitivity to the active substance or any other excipients listed in section 6.1.

4.4 Warnings and precautions for use

Warnings and precautions applicable to type 1 hepatorenal syndrome
Prior to treatment of type 1 hepatorenal syndrome, other types of acute kidney injury should be ruled out.

Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442 µmol/L (5.0 mg/dL), when treated with terlipressin for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of adverse events, and increased mortality in this patient group have been observed in clinical trials (see section 4.2).

Hepatic impairment
Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥ 39, when treated with terlipressin for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of respiratory failure, and increased mortality in this patient group have been observed in clinical trials (see section 4.2).

Respiratory events
Fatal cases of respiratory failure, including respiratory failure due to fluid overload, have been reported in patients treated with terlipressin for type 1 hepatorenal syndrome.

Patients with a new onset of breathing difficulties or worsening of respiratory disease should be stabilised prior to receiving their first dose of terlipressin.

Caution should be exercised when terlipressin is administered together with human albumin as part of the standard of care for type 1 hepatorenal syndrome. In case of signs or symptoms of respiratory

failure or fluid overload, dose reduction of human albumin should be considered. If respiratory symptoms are severe or do not resolve, treatment with terlipressin should be discontinued.

Sepsis/ septic shock
Cases of sepsis/septic shock, including fatal cases, have been reported in patients treated with terlipressin for type 1 hepatorenal syndrome. Causal association to terlipressin has not been established. Patients should be monitored daily for any signs or symptoms suggestive of infection.

Warnings and precautions applicable to all indications
Monitoring during treatment
During treatment, regular monitoring of blood pressure, ECG or heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance are required.

Patient with cardiovascular and pulmonary disease
Particular care is required in management of patients with cardiovascular or pulmonary disease since terlipressin may induce ischaemia and pulmonary vascular congestion. Caution should also be exercised in treating patients with hypertension.

Patients with septic shock
In patients with septic shock with a low cardiac output terlipressin should not be used.

Injection site reaction
To avoid local necrosis at the injection site, the injection must be given IV.

Skin necrosis
During post-marketing experience with terlipressin several cases of cutaneous ischaemia and necrosis unrelated to the injection site have been reported (see section 4.8). Patients with diabetes mellitus and obesity seem to have a greater tendency to this reaction. Therefore, caution should be exercised when administering terlipressin in these patients.

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, electrolytic abnormalities, or concomitant medications that can prolong the QT interval (see section 4.5).

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.

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

Sodium content
This medicinal product contains 30.7 mg of sodium per ampoule, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 hypomagnesemia (e.g. some diuretics).

4.6 Fertility, pregnancy and lactation

Fertility
No human data on the effects of terlipressin on fertility is available. Animal studies do not indicate harmful effects of terlipressin on male fertility (see section 5.3).

Pregnancy
Treatment with terlipressin during pregnancy is contraindicated (see sections 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 have been shown in rabbits after treatment with Terlipressin.

Lactation
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 frequently reported undesirable effects in clinical trials are abdominal pain, nausea, diarrhoea, pallor, dyspnoea (for type 1 HRS), respiratory failure (for type 1 HRS), vomiting, andbradycardia.

The antidiuretic effect of terlipressin may cause hyponatraemia unless the fluid balance is controlled. There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications.

Tabulated summary of adverse reactions

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Frequency not known[a]
Infections and infestations		Sepsis/septic shock[b, c]		
Metabolism and nutrition disorders		Hyponatraemia		
Nervous system disorders		Headache		
Cardiac disorders		Chest pain Bradycardia Tachycardia	Atrial Fibrillation Ventricular extrasystoles[d] Myocardial Infarction Torsade de pointes Cardiac failure	
Vascular disorders		Vasoconstriction Peripheral ischemia Pallor Hypertension Cyanosis	Hot flush	
Respiratory, thoracic and mediastinal disorders	Respiratory failure[b] Dyspnoea[b]	Pulmonary oedema Respiratory distress[b] Dyspnoea[e]	Respiratory distress[e] Respiratory failure[e]	
Gastrointestinal disorders	Abdominal pain	Diarrhoea Nausea Vomiting	Intestinal ischaemia	
Skin and subcutaneous tissue disorders			Skin necrosis (unrelated to the site of administration)*[c, d]	
Pregnancy, puerperium and perinatal conditions				Uterine hypertonus
Reproductive system and breast disorders				Uterine ischaemia
General disorders and administration site disorders			Injection site necrosis	

[a] Frequencies of these adverse events cannot be estimated from the available data.
[b] Applicable to type 1 hepatorenal syndrome. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials.
[c] See section 4.4 for further information
[d] Adverse reactions identified from post-marketing sources are presented by frequency category based on a theoretically calculated frequency if not observed in clinical trials.
[e]Applicable to Bleeding Oesophageal Varices

Description of selected adverse reactions

Safety related to method of administration

Based on results from a dedicated randomised controlled multicentre trial, administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see section 4.2 and 5.1).

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 in the specific patient population 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 IV.

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 (Triglycyl-Lysine-Vasopressin) is a synthetic analogue of the natural posterior pituary hormone vasopressin.

Terlipressin is a pro-drug with partial, intrinsic activity by itself. Terlipressin is transformed into the fully active metabolite lysine-vasopressin (LVP) by enzymatic cleavage. 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 with a sustained effect throughout the treatment period of 4 to 6 hours.

Bleeding oesophageal varices

The pathophysiology of bleeding oesophageal varices is caused by the haemodynamic changes induced by portal hypertension leading to redirection of blood flow to blood vessels in the walls (lamina propria, submucosa) of the upper gastric and lower oesophageal regions resulting in the development of oesophageal varices. Terlipressin and its metabolites exert their effects via the vasopressin-1a receptor in vascular smooth muscle to induce splanchnic arterial vasoconstriction which results in a decrease of the portal pressure. Consequently, an improvement of the systemic circulatory function and redistribution of the effective arterial blood volume is observed.

Hepatorenal syndrome

The pathophysiology of type 1 hepatorenal syndrome is caused by the haemodynamic changes induced by portal hypertension seen in advanced cirrhosis. Terlipressin and its metabolites exert their effects via the vasopressin-1α receptor in vascular smooth muscle to induce splanchnic arterial vasoconstriction which results in a decrease of the portal pressure. Consequently, an improvement of the systemic circulatory function and redistribution of the effective arterial blood volume is observed. Lowering of portal pressure together with the improved systemic circulation leads to the suppression of the activity of the renin-angiotensin system and sympathetic nervous system, which are major triggers of excessive renal vasoconstriction, causing type 1 hepatorenal syndrome.

Clinical efficacy and safety

Continuous intravenous infusion versus intravenous boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis

The safety of continuous intravenous infusion of terlipressin has been compared with intravenous bolus in an open-label randomised controlled multicentre trial. Seventy-eight patients with type 1 hepatorenal syndrome were randomly assigned to either continuous intravenous infusion at the initial dose of 2 mg/day or intravenous boluses of terlipressin at the initial dose of 0.5 mg every 4 hours. In case of no

response, the dose was progressively increased to a final dose of 12 mg/day in both groups. Albumin was given at the same dose in both groups. The primary endpoint was defined as the prevalence of treatment-related adverse events (AEs) between the two groups. Both the total rate of treatment-related AEs as well as severe treatment-related AEs were lower in the continuous infusion group than in the bolus group (all treatment-related AEs: 12/34 patients (35%) vs 23/37 patients (62%), $p<0.025$. Severe treatment-related AEs: 7/34 patients (21%) vs 16/37 patients (43%); $p<0.05$). The rate of response to terlipressin was not statistically significantly different between the continuous infusion and bolus groups (76% vs 65%). The probability of 90-day transplant-free survival was not significantly different between the continuous infusion group and the bolus group (53% vs 69%).

5.2 Pharmacokinetic properties
The pharmacokinetics of terlipressin follows a two-compartment model with a rapid distribution phase.

Absorption
Terlipressin is administered by the intravenous route resulting in instant systemic exposure.

Distribution
In patients with liver cirrhosis with or without hepatorenal syndrome the mean distribution volume was reported in the range 0.2 to 0.5 l/kg in two clinical trials.

Biotransformation
The concentration of the active metabolite, lysine-vasopressin, starts to increase approximately 30 minutes after bolus administration of terlipressin and peak levels are reached between 60 and 120 minutes after administration of terlipressin.

Elimination
The terminal elimination half-life of terlipressin is approximately 40 minutes in patients with liver cirrhosis with and without hepatorenal syndrome and the mean clearance was reported in the range 5 to 9 ml/kg/min in two clinical trials.

Linearity
Terlipressin demonstrated a dose-dependent and approximate proportional increase in total exposure (AUC) after single IV injections to healthy subjects (n=2-14 subjects per dose group) in a dose range between 5 and 30 µg/kg.

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 but as the route of administration was intravenous, systemic exposure at multiples of the maximum human dosages 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.

In a rat fertility study, mating of terlipressin-treated males with untreated females had no effect on the number of matings and frequency of insemination but led to decreased post-natal litter size. Testicular atrophy and disturbances of spermiogenesis observed in male rats treated with terlipressin for 3 weeks could not be confirmed. Likewise no testicular effects were seen in any other repeat-dose toxicity study in rats and dogs.

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 except for those stated in section 6.7.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in a refrigerator (2 °C - 8 °C). Store in the original package 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.

6.7 Other handling information
For intravenous infusion
The terlipressin daily dose can be diluted using aseptic techniques in up to 250 mL of sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5 %) before administration. The diluted solution is stable for up to 24 hours at 25 °C.

7. **MANUFACTURER**

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