Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

GLYPRESSIN 1 mg Powder and Solvent for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 1 mg terlipressin acetate.

Excipients with known effect
One vial contains 0.77 mmol (17.7 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White, sterile powder.

Clear, colourless solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in the short term management of bleeding oesophageal varices.

"Emergency treatment of type 1 hepatorenal syndrome, as defined by IAC (International Ascites Club) criteria".

4.2 Posology and method of administration

1) Short term management of bleeding oesophageal varices
Adults:
Initially an i.v. injection of 2 mg terlipressin acetate 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 terlipressin acetate i.v. every 4 hours in patients with body weight < 50 kg or if adverse effects occur.

2) In type 1 hepatorenal syndrome
3 to 4 mg every 24 hours as 3 or 4 administrations. In the absence of any reduction of the serum creatinine after 3 days of treatment, cessation of Glypressin treatment is advised. As an alternative to bolus injection, terlipressin can be administered as a continuous intravenous (IV) infusion with a starting dose of 2 mg of terlipressin acetate/24 hours and increased to a maximum of 12 mg of terlipressin acetate/24 hours. 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 5.1).
In other cases, Glypressin treatment is to be pursued until the obtaining either of a serum creatinine less than 130 µmol/litre or of a drop of at least 30% in the serum creatinine with respect to the value measured at the time of diagnosis of hepatorenal syndrome.

<u>The standard average duration of treatment is 10 days</u>
<u>Special Populations</u>
Elderly patients
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.

Type 1 hepatorenal syndrome

Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/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).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Contraindicated in pregnancy.

4.4 Special warnings and precautions for use

Type 1 hepatorenal syndrome
Prior to use of terlipressin for hepatorenal syndrome, it must be ascertained that the patient has an acute functional renal failure and this functional renal failure does not respond to a suitable plasma expansion therapy.

Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/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. Patients should be monitored daily for any signs or symptoms suggestive of infection.

Monitoring during treatment
During treatment regular monitoring and control of blood pressure, ECG or heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance are required. Particular care is required in management of cardiovascular or pulmonary disease since terlipressin may induce ischemia and pulmonary vascular congestion.

Caution should be exercised in treating patients with hypertension, recognised heart disease, renal dysfunction, cerebral or peripheral vascular disease, asthma or respiratory failure.

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 administered intravenously.

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

Paediatric population and elderly patients
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.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Pregnancy
Treatment with GLYPRESSIN during pregnancy is contraindicated (see sections 4.3 and 5.3). 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 foetus.

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

Breast-feeding
It is not known whether GLYPRESSIN is excreted in human breast milk. The excretion of GLYPRESSIN 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 GLYPRESSIN should be made taking into account the benefit of breast-feeding to the child and the benefit of GLYPRESSIN 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 most frequently reported undesired effects in clinical trials are paleness, increased blood pressure, abdominal pain, nausea, diarrhoea, and headache.

Tabulated list of adverse reactions
There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications.

MedDRA System Organ Class	**VERY**	**COMMON**	**UNCOMMON**	**RARE**

	COMMON (<1/10)	(≥1/100 to <1/10)	(≥1/1,000 to <1/100)	(≥1/10,000 to <1/1,000)
Metabolism and nutrition disorders			Hyponatraemia	
Nervous system disorders		Headache		
Cardiac disorders		Bradycardia	Atrial Fibrillation Ventricular Extracystoles Tachycardia Myocardial Infarction Torsade de pointes Cardiac failure Cyanosis	
Vascular disorders		Vasoconstriction Peripheral ischaemia Pallor Hypertension	Hot flush	
Respiratory, thoracic and mediastinal disorders	Respiratory failure[a] Dyspnoea[a]	Pulmonary oedema[a] Respiratory distress[a]	Respiratory distress[b] Respiratory failure[b] Pulmonary oedema[b]	Dyspnoea[b]
Gastrointestinal disorders		Abdominal pain Diarrhoea	Nausea Vomiting Intestinal ischaemia	
Skin and subcutaneous tissue disorders			Skin necrosis	
Pregnancy, puerperium and perinatal conditions			Uterine hypertonus Uterine ischaemia	
General disorders and administration site disorders			Injection site necrosis Chest pain	
SOC Infections and infestations		Sepsis / septic shock[a]		

[a] Applicable to type 1 hepatorenal syndrome. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials.
[b]Applicable to other approved indications apart from type 1 hepatorenal syndrome.

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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

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 hypertension can be controlled with clonidine 150 µg iv. Severe bradycardia should be treated with atropine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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. LVP remains within the therapeutic concentration range over a period of 4-6 hours.

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 terlipressin acetate with a sustained effect throughout the treatment period (4 to 6 hours).

Clinical efficacy and safety
Continuous IV infusion versus IV boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis.
The safety of continuous IV infusion of terlipressin has been compared with IV bolus in an open-label randomised controlled multicentre trial. Seventy-eight patients with type 1 hepatorenal syndrome were randomly assigned to either continuous IV infusion of terlipressin acetate at the initial dose of 2 mg/day or IV boluses of terlipressin acetate 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

GLYPRESSIN is administered by bolus i.v. injection. It shows a biphasic plasma level curve which indicates that a two compartment model can be applied. The half life of Distribution (T 1/2α) is about 8-10 minutes. The half-life of elimination (T ½ β) is about 50-70 minutes.

Lysine vasopressin reaches maximum plasma levels about 1-2 hours following i.v. administration and has a duration of activity of 4-6 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection (vial)

Mannitol
Hydrochloric acid (for pH-adjustment)

Solvent (ampoule)

Sodium chloride
Hydrochloric acid (for pH-adjustment).
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

Unopened: 3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

The reconstituted solution must be used immediately after reconstitution.

6.5 Nature and contents of container

Type I glass vial with bromobutyl rubber stopper and type I glass ampoule.

The vial contains terlipressin acetate 1 mg. The ampoule has a coloured dot indicating the cut area and contains 5 ml of clear, colourless solvent.

Pack size: 5 sets of 1 vial + 1 ampoule.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Reconstitute GLYPRESSIN with the solvent provided immediately prior to use. For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

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United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1009/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th April 1987

Date of last renewal: 9th April 2007

10 DATE OF REVISION OF THE TEXT

March 2023