1. NAME OF THE MEDICINAL PRODUCT

Glypressin 1 mg/ 8.5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

8.5 ml of injection solution contains 1mg Terlipressin Acetate (0.12 mg/ml).

Excipients with known effect
One ampoule contains 30.7 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless aqueous fluid.

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 (2 x 8.5 ml) 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 (8.5 ml) 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:

An i.v. injection 3 to 4 mg (3x8.5ml to 4x8.5ml) terlipressin acetate 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.
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.

The standard average duration of treatment is 10 days.

Special Populations

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.

Method of Administration
IV injection

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

Cardiac, pulmonary and vascular disease
During treatment regular monitoring and control of blood pressure, ECG, heart rate, serum levels of sodium and potassium, as well as fluid balance are required.
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).

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.

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 medicinal product contains 1.33 mmol (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 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 reflexofenic inhibition of the cardiac activity via the vagus nerve due to 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 the uterine blood flow. Glypressin may have harmful effects on pregnancy and foetus.

Spontaneous abortion and malformation of the foetus 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

MedDRA System Organ Class	**COMMON** **(≥1/100 to <1/10)**	**UNCOMMON** **(≥1/1,000 to <1/100)**	**RARE** **(≥1/10,000 to <1/1,000)**
Metabolism and nutrition disorders		Hyponatraemia	
Nervous system	Headache		

disorders			
Cardiac disorders	Bradycardia	Atrial Fibrillation Ventricular Extracystoles Tachycardia Myocardial Infarction Torsades de pointe Cardiac failure Cyanosis	
Vascular disorders	Vasoconstriction Peripheral ischaemia Pallor Hypertension	Hot flush	
Respiratory, thoracic and mediastinal disorders		Respiratory distress Respiratory failure Pulmonary oedema	Dyspnoea
Gastrointestinal disorders	Abdominal pain Diarrhoea	Nausea Vomiting Intestinal ischaemia Transient vomiting	
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	

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 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: 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).

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 (T1/2) is about 8-10 minutes.
The half-life of elimination (T1/2) 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

Sodium chloride
Acetic acid
Sodium acetate
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 (2-8°C). Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each carton contains five clear hydrolytic class 1 glass ampoules, 10ml nominal volume. The ampoule has a coloured dot indicating the cut area. It contains 8.5ml of solution for injection.

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

Each ampoule is for single use only. Discard any unused solution.

7. MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd.
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin24

8. MARKETING AUTHORISATION NUMBER

PA 1009/4/2

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 25th September 2009
Date of last renewal: 25th September 2014

10. DATE OR REVISION OF THE TEXT

July 2020