NEW ZEALAND DATA SHEET

1 PRODUCT NAME

TERLIPRESSIN EVER PHARMA 1 mg/5 mL solution for injection
TERLIPRESSIN EVER PHARMA 2 mg/10 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mL of injection solution contains 1 mg terlipressin acetate corresponding to 0.85 mg terlipressin,
10 mL of injection solution contains 2 mg terlipressin acetate corresponding to 1.7 mg terlipressin.

Each mL contains 0.2 mg terlipressin acetate corresponding to 0.17 mg terlipressin.

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Solution for injection. Clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TERLIPRESSIN EVER PHARMA is indicated in for the treatment of:

- Bleeding Osesophageal Varices (BOV)
- Type 1 Hepatorenal Syndrome, characterised by spontaneous acute renal insufficiency, in patients suffering from severe cirrhosis, with ascites.

4.2 Dose and method of administration

Bleeding Oesophageal Varices
An intravenous injection of 2mg terlipressin acetate 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 terlipressin acetate every 4 hours in patients with a body weight of less than 50kg or when necessitated by adverse effects.

Type 1 Hepatorenal Syndrome
3-4mg terlipressin acetate every 24 hours as 3 or 4 administrations.

If serum creatinine does not decrease at least 25% after 3 days, the dose can be increased in a stepwise manner up to a maximum of 2mg terlipressin acetate every 4 hours.

In the other cases, TERLIPRESSIN EVER PHARMA treatment is to be pursued until the obtaining either of a serum creatinine less than 130µmol/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.

TERLIPRESSIN EVER PHARMA must only be administered intravenously

4.3 Contraindications

- Pregnancy
- Septic shock with low cardiac output
- Hypersensitivity to terlipressin or any other excipients of the product listed in section 6.1.

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 intravenously. Caution should be exercised in treating patients with hypertension, recognised heart disease, or peripheral artery disease. The effectiveness of terlipressin in the treatment of hepatorenal syndrome with concomitant sepsis is unknown. In patients with septic shock with a low cardiac output terlipressin should not be used.

This product contains 0.77 mmol (or 17.7 mg) sodium per 5 mL vial and 1.54 mmol (or 35.4 mg) sodium per 10 mL vial. This should be taken into consideration in patients on a controlled sodium diet.

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.

4.5 Interaction with other medicines 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with terlipressin during pregnancy is contraindicated. 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 on the foetus.

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

Breastfeeding

It is not known whether terlipressin is excreted in human 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.

Fertility
No information available.

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

Summary of safety profile
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 terlipressin may cause hyponatraemia unless fluid balance is controlled.

Tabulated summary of adverse reactions

System Organ Class Disorder	COMMON (1/100 to <1/10)	UNCOMMN (1/1,000 to <1/100)	RARE (1/10,000 to <1/1,000)
Metabolism		Hyponatraemia if fluid not monitored	
Nervous System	Headache		
Cardiac	Bradycardia	Atrial Fibrillation Ventricular extracystoles Tachycardia Chest pain Myocardial Infarction Fluid overload with pulmonary oedema Torsade de pointes Cardiac failure	
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 Uterine ischaemia	
General disorders and administration site disorders		Injection site necrosis	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
The recommended dose (2mg terlipressin acetate) every 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 150mcg clonidine intravenous. Bradycardia requiring treatment should be treated with atropine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
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. Terlipressin acetate given at doses of 1mg and 2mg effectively reduces 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 terlipressin acetate is more effective than 1mg 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 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 terlipressin. 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-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Hydrochloric acid
Sodium chloride
Sodium hydroxide
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

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Supplied in colourless glass vials, closed with rubber stopper and sealed with aluminium flip-off cap.

Each vial contains 5 mL or 10 mL of solution.

Pack sizes:
1x 5 mL, 5 x 5 mL
1 x 10 mL, 5 x 10 mL

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd
t/a Healthcare Logistics
On behalf of InterPharma Pty Ltd
58 Richard Pearse Drive
Airport Oaks, Mangere 2022
Auckland, New Zealand

9 DATE OF FIRST APPROVAL

1 April 2020