SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terlipressin Acetate EVER Pharma 0.2 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.2 mg terlipressin acetate corresponding to 0.17 mg terlipressin.
Each vial of 5 ml solution contains terlipressin acetate 1 mg corresponding to 0.85 mg terlipressin.
Each vial of 10 ml solution contains terlipressin acetate 2 mg corresponding to 1.7 mg terlipressin

Excipients with known effect:
This medicinal product contains 0.8 mmol (18.4 mg) sodium per 5 ml dose and 1.6 mmol (36.8 mg) sodium per 10 ml dose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution with a pH of 4.0 – 5.0 and an osmolarity of 270 – 330 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bleeding oesophageal varices.
Treatment of type I hepatorenal syndrome.

4.2 Posology and method of administration

1) Oesophageal varices bleeding

Unless otherwise prescribed, initially IV injection of 1-2mg terlipressin acetate, equivalent to 1 vials of 5 ml or 1 vial of 10 ml of Terlipressin 1mg, is slowly administered to adults. The maintenance dose is 1 mg terlipressin acetate, equivalent to 1 vial of Terlipressin 1mg after 4-6 hours. The standard value of the maximum daily dose of Terlipressin is 120-150 ug/kg body weight. For an adult person of 70 kg body weight, this corresponds to a dose of 8- 10 vials of 1 mg per day, to be administered in 4-hour intervals.

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 Terlipressin treatment is advised.
In the other cases, Terlipressin 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 terlipressin or any other excipient of the product.

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.

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.

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.

Injection site reaction

To avoid local necrosis at the injection site, the injection must be administered intravenously.

Septic shock

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

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 medicinal product contains 0.8 mmol (18.4 mg) sodium per 5 ml dose and 1.6 mmol (36.8 mg) sodium per 10 ml dose. To be taken into consideration by patients on a controlled sodium diet.

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 Pregnancy and lactation

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.

Breast-feeding
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 most commonly 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 (<1/10)**	**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 disorders		Headache		

Cardiac disorders		Bradycardia	Atrial fibrillation Ventricular extracystoles Tachycardia Myocardial infarction Torsade de pointes Cardiac failure Cyanosis	
Vascular disorders		Vasoconstriction Peripheral ischemia Pallor Hypertension	Hot flush	
Respiratory, thoracic and mediastinal disorders	Respiratory failure[a] Dyspnoea[a]	Respiratory distress[a] Pulmonary oedema[a]	Respiratory distress[b] Pulmonary oedema[b] Respiratory failure[b]	Dyspnoea[b]
Gastrointestinal disorders		Abdominal pain Diarrhoea	Nausea Intestinal ischemia 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 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

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).

5.2 Pharmacokinetic properties
Terlipressin is administered by bolus IV injection. It shows a biphasic plasma level curve which indicates that a two-compartment model can be applied. The half-life of Distribution (T ½ α) 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
Sodium Chloride
Acetic Acid
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injectionsIncompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.2 Shelf life
The expiry date of the product is indicated on the packaging materials.
Once the vial has been opened, the product must be used immediately

6.3 Special precautions for storage
Store in a refrigerator at 2-8°C. Do not freeze. Store the vial in the outer carton.

6.4 Nature and contents of container
Colourless glass vials with bromobutyl rubber stopper and sealed with aluminium flip-off cap.
Each vial contains 5 ml of solution.
Pack size: 1 x 5 ml ampoule, 1 x 10 ml ampoule
Not all presentations are available in Israel.

6.5 Special precautions for disposal and other handling
For single use only.
Store in the original package in order to protect from light.
No special requirements.
Discard any unused solution.
Any unused medicinal product or waste should be disposed of in accordance with local requirements.

7. **Manufacturer:**
EVER Valinject GmbH, Oberburgau 3, 4866 Unterach am Attersee, Austria.

8. License Holder and Importer:
Pharmalogic Ltd., 14 Imber St., Petah-Tikva 49511.

10. Registration number:

Revised on November 2025 according to MOH guidelines.