Package leaflet: Information for the patient

Terlipressin acetate EVER Pharma 0.2 mg/ml Solution for injection

terlipressin acetate

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Terlipressin acetate EVER Pharma is and what it is used for

Terlipressin acetate EVER Pharma contains the active ingredient terlipressin, which is a synthetic pituitary hormone (this hormone is usually produced by the pituitary gland found in the brain).
It will be given to you by injection into a vein.
Terlipressin acetate EVER Pharma is used for the treatment of:
- bleeding from dilated (widening) veins in the food pipe leading to your stomach (called bleeding oesophageal varices).
- emergency treatment of type 1 hepatorenal syndrome (rapidly progressive renal failure) in patients with liver cirrhosis (scarring of the liver) and ascites (abdominal dropsy).

2. What you need to know before you are given Terlipressin acetate EVER Pharma

You should not receive Terlipressin acetate EVER Pharma:
- If you are allergic to terlipressin or any of the other ingredients of this medicine (listed in section 6)
- If you are pregnant.

Warnings and precautions
Talk to your doctor or nurse before you are given Terlipressin acetate EVER Pharma:

- If you have a severe infection known as septic shock
- If you have bronchial asthma or other conditions that affect your breathing
- If you have uncontrolled high blood pressure, insufficient blood circulation in the heart vessels (e.g. angina)
- If you have previously had a heart attack (myocardial infarction), or you have hardening of the arteries (arteriosclerosis)
- If you suffer from seizures (convulsions)
- If you have irregular heart beats (cardiac arrhythmias) or a history of QT interval prolongation (disturbance of heart rhythm)
- If you have a poor blood circulation to your brain (e.g. you have had a stroke) or to your limbs (peripheral vascular disease)
- If you have an impaired kidney function (renal insufficiency)
- If you have disturbances in the level of salt (electrolytes) in your blood
- If you have reduced amount of fluid in your circulation or have already lost a large amount of blood
- If you are over the age of 70 years.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Terlipressin acetate EVER Pharma.

During treatment with Terlipressin acetate EVER Pharma your heart function and fluid and electrolyte balance should be monitored constantly.

Terlipressin acetate EVER Pharma can increase your risk of developing respiratory failure (severe breathing difficulties) that may be life-threatening. If you experience difficulty breathing, or symptoms of fluid overload, before Terlipressin acetate EVER Pharma is given or during treatment immediately inform your doctor.

If you are treated for very severe liver and kidney disease (type 1 hepatorenal syndrome), your doctor should ensure that your heart function and fluid and electrolyte balance are monitored during the treatment.

Particular care is required if you have prior heart or lung disease since Terlipressin acetate EVER Pharma can induce heart ischemia (decrease in the amount of blood flow to the heart) and respiratory failure.

Treatment with Terlipressin acetate EVER Pharma should be avoided if you have liver failure with multiple organ failures and/or kidney failure with very high levels of creatinine (a waste product) in the blood, as it increases your risk of adverse outcomes.

If you are treated for very severe liver and kidney disease, Terlipressin acetate EVER Pharma can increase your risk of developing sepsis (bacteria in the blood and the body's extreme response to an infection) and septic shock (a serious condition that occurs when a major infection leads to low blood pressure and low blood flow). Your doctor will take additional precautions should this apply to you.

Children and adolescents
Terlipressin acetate EVER Pharma is not recommended for use in children and adolescents due to insufficient experience.

Other medicines and Terlipressin acetate EVER Pharma
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Please inform your doctor immediately if you take any of the following medicines:
-drugs that have an effect on your heart rate (e.g. beta-blockers, sufentanil or propofol)
-drugs that can trigger irregular beating of the heart (arrhythmia) such as the following:

- anti-arrhythmic drugs known as Class IA (quinidine, procainamide, disopyramide) and Class III (amiodarone, sotalol, ibutilide, dofetilide)
- erythromycin (an antibiotic)
- antihistamines (mainly used to treat allergies but also found in certain cough and cold remedies)
- tricyclic antidepressants used to treat depression
- medicines that may alter the level of salt or electrolytes in your blood, particularly diuretics (water tablets used to treat high blood pressure and heart failure)

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

Terlipressin acetate EVER Pharma must not be used during pregnancy.

It is not known if Terlipressin acetate EVER Pharma is present in breast milk, therefore the possible effects on your baby are unknown. You should discuss the potential risk to your baby with your doctor.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, if you feel unwell after receiving the injection, do not drive or operate machinery.

Terlipressin acetate EVER Pharma contains sodium
This medicine contains 3.68 mg sodium (main component of cooking/table salt) in each ml. This is equivalent to 0.18 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Terlipressin acetate EVER Pharma will be given

This medicine is injected or infused intravenously by a doctor. The doctor will decide the most appropriate dose for you and your heart and blood circulation will be continuously monitored during administration. Please ask your doctor for further information regarding its use.

Use in adults
1. Short term management of bleeding oesophageal varices
Initially 1-2 mg terlipressin acetate (5-10 ml of Terlipressin acetate EVER Pharma) is given by injection into your vein. Your dose will depend on your body weight.
After the initial injection, your dose may be reduced to 1 mg terlipressin acetate (5 ml) every 4 to 6 hours.

2. Type 1 hepatorenal syndrome
The usual dose for injection is 1 mg terlipressin acetate every 6 hours for at least 3 days. If the reduction of serum creatinine is less than 30 % after 3 days of treatment your doctor should consider doubling the dose to 2 mg every 6 hours.

You may also be given Terlipressin acetate EVER Pharma as a drip (continuous intravenous infusion) usually starting with 2 mg terlipressin acetate per day and increased in a stepwise manner to a maximum of 12 mg terlipressin acetate per day.

If there is no response to Terlipressin acetate EVER Pharma or in patients with complete response, treatment with Terlipressin acetate EVER Pharma should be interrupted.
When a reduction in serum creatinine is seen, treatment with Terlipressin acetate EVER Pharma should be maintained to a maximum of 14 days.

Use in the elderly
If you are over 70 years of age speak with your doctor before you receive Terlipressin acetate EVER Pharma.

Use in patients with kidney problems
Terlipressin acetate EVER Pharma should be used with caution in patients with long standing kidney failure.

Use in patients with liver problems
No dose adjustment is required in patients with liver failure.

Use in children and adolescents
Terlipressin acetate EVER Pharma is not recommended for use in children and adolescents due to insufficient experience.

Duration of treatment
The use of this medicine is limited to 2 – 3 days for short term management of bleeding oesophageal varices and to a maximum of 14 days for treatment of type 1 hepatorenal syndrome, depending on the course of your condition.

If you are given more Terlipressin acetate EVER Pharma than you should
As this medicine is given by a healthcare professional, it is unlikely you will be given more than the recommended dose. If you are given too much you may have a rapid increase in your blood pressure (this will be noticed during the continuous monitoring), especially if you already suffer with high blood pressure. If this happens then you will be given another medicine called an alpha blocker (e.g. clonidine) to control your blood pressure.

If you experience lightheadedness, dizziness, or feeling faint, tell your doctor because these could be signs of a low heart rate. This can be treated with another medicine called atropine.

If you stop using Terlipressin acetate EVER Pharma

Your doctor will advise when it is time to stop receiving this medicine.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects which need immediate attention:

In very rare cases, there may be severe side effects when you are given Terlipressin acetate EVER Pharma.
If you are affected by any of the following side effects, **please tell your doctor immediately** if you are able to. Your doctor should not give you any more Terlipressin acetate EVER Pharma.

- severe shortness of breath due to an asthma attack
- severe pain in the chest (angina)
- severe and persistent irregular heart beats
- dead skin around the injection site (necrosis)
- convulsions (seizure)

Tell your doctor or other healthcare professional straight away:

- if you develop breathing difficulties or experience a worsening of breathing ability (signs or symptoms of respiratory failure). This side effect is very common if you are treated for type 1 hepatorenal syndrome - may affect more than 1 in 10 people.
- if you develop signs or symptoms of infection of the blood (sepsis/septic shock), which may include fever and chills or very low body temperature, pale and/or bluish skin, severe breathlessness, urinating less than usual, fast heartbeat, nausea and vomiting, diarrhoea, fatigue and weakness, and feeling dizzy. This side effect is common if you are treated for type 1 hepatorenal syndrome - may affect up to 1 in 10 people.

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Other side effects that may occur with different frequencies depending on the disease that you have.

Very common (may affect more than 1 in 10 people):

If you have type 1 hepatorenal syndrome:

- shortness of breath (dyspnoea)

Common (may affect up to 1 in 10 people):

- very slow heart rate
- signs of insufficient blood circulation in the heart vessels in the ECG
- high or low blood pressure
- insufficient blood circulation in arms, legs and skin
- paleness of face
- pale skin
- headache
- temporary abdominal cramps
- temporary diarrhoea
- abdominal cramps (in women)

Tell your doctor or other healthcare professional straight away:
If you have type 1 hepatorenal syndrome:

- fluid in the lungs (pulmonary oedema)
- difficulties in breathing (respiratory distress)

Uncommon (may affect up to 1 in 100 people):

- chest pain
- rapid increase in blood pressure
- heart attack
- too fast heart rate (palpitations)
- swelling of the tissues in the body or fluid on the lungs
- bluish colouration of the skin or lips

- hot flushes
- temporary nausea
- temporary vomiting
- reduced blood supply to the intestinal system
- inflammation of the lymph vessels – seen as fine red streaks under your skin extending from the affected area to the armpit or groin and by fever, chills, headache, and muscle pain
- too little sodium in the blood (hyponatraemia)

Tell your doctor or other healthcare professional straight away:
If you have dilated (widening) veins in the food pipe:
- fluid in the lungs (pulmonary oedema)
- difficulties in breathing (respiratory distress)

Rare (may affect up to 1 in 1,000 people):
- stroke
- too much sugar in the blood (hyperglycaemia)

Tell your doctor or other healthcare professional straight away:
If you have dilated (widening) veins in the food pipe:
- shortness of breath (dyspnoea)

Not known: frequency cannot be estimated from the available data
- heart failure
- Torsade de Pointes
- dead skin (necrosis) in areas other than at the injection site
- decreased blood flow to the uterus
- uterine cramps (cramps in the womb)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Terlipressin acetate EVER Pharma

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2˚C-8°C). Do not freeze.

The solution should be inspected visually for particles and discolouration prior to administration. The medicine must not be used if any discolouration is noticed. Do not throw away any medicines via wastewater or household waste. The doctor will dispose of this medicine. These measures will help protect the environment.

6. Contents of the pack and other information

What Terlipressin acetate EVER Pharma contains

- the **active** substance is terlipressin acetate.
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.
This is equivalent to 0.2 mg terlipressin acetate per ml, corresponding to 0.17 mg terlipressin per ml.

- the **other ingredients** are: Sodium chloride, acetic acid, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment) and water for injections

What Terlipressin acetate EVER Pharma looks like and contents of the pack

This medicine is supplied in a clear glass vial containing 5 ml or 10 ml of a clear, colourless solution.

This medicine is available in pack sizes of: 1 x 5 ml, 5 x 5 ml, 1 x 10 ml, 5 x 10 ml

Not all pack sizes may be marketed.

Marketing Authorisation Holder
EVER Valinject GmbH
Oberburgau 3
4866 Unterach am Attersee
Austria

Manufacturer
EVER Pharma Jena GmbH
Otto-Schott-Strasse 15
07745 Jena
Germany

EVER Pharma Jena GmbH
Brüsseler Str. 18
07747 Jena
Germany

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

AT Terlipressinacetat EVER Pharma 0,2 mg/ml Injektionslösung
BG Терлипресин ацетат EVER Pharma 0,2 mg/ml инжекционен разтвор
CZ Terlipresin acetát EVER Pharma
DE Terlipressinacetat EVER Pharma 0,2 mg/ml Injektionslösung
ES Terlipresina acetato EVER Pharma 1 mg solución inyectable
Terlipresina acetato EVER Pharma 2 mg solución inyectable
FR ACETATE DE TERLIPRESSINE EVER PHARMA 0,2 mg/ml, solution injectable
IE Terlipressin acetate EVER Pharma 0.2 mg/ml solution for injection
IT Terlipressina acetato EVER Pharma
PL Terlipressini acetas EVER Pharma
PT Terlipressina EVER Pharma, 0,2 mg/ml, Solução injetável
RO Acetat de Terlipresină EVER Pharma 0,2 mg/ml soluţie injectabilă
SK Terlipresín EVER Pharma 0,2 mg/ml injekčný roztok
UK Terlipressin acetate EVER Pharma 0.2 mg/ml solution for injection

This leaflet was last revised in July 2023.

The following information is intended for healthcare professionals only

Posology

1) Short term management of bleeding oesophageal varices:
Initial dose: 1 to 2 mg terlipressin acetate[#] (equivalent to 5 to 10 ml solution) is administered by intravenous injection over a period of one minute.

Depending on the patient's body weight the dose can be adjusted as follows:

- weight less than 50 kg: 1 mg terlipressin acetate (5 ml)
- weight 50 kg to 70 kg: 1.5 mg terlipressin acetate (7.5 ml)
- weight exceeding 70 kg: 2 mg terlipressin acetate (10 ml).

Maintenance dose: After the initial injection, the dose can be reduced to 1 mg terlipressin acetate every 4 to 6 hours.

[#] 1 to 2 mg terlipressin acetate corresponding to 0.85 to 1.7 mg terlipressin

The approximate value for the maximum daily dose of Terlipressin acetate EVER Pharma is 120 micrograms terlipressin acetate per kg body weight.

The therapy is to be limited to 2 to 3 days depending on the response to treatment and the course of the disease.

Terlipressin acetate EVER Pharma is injected intravenously and should be given over a period of one minute.

2) In type 1 hepatorenal syndrome:

An i.v. injection of 1 mg terlipressin acetate every 6 hours for at least 3 days. If after 3 days of treatment, the decrease of serum creatinine is less than 30 % with respect to the baseline, doubling the dose to 2 mg every 6 hours will have to be considered.

As an alternative to bolus injection, terlipressin can be administered as a continuous i.v. 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 i.v. infusion may be associated with lower rates of severe adverse events than with administration by i.v. bolus.

Treatment with terlipressin should be interrupted if there is no response to treatment (defined as decrease of serum creatinine is less than 30 % on day 7 with respect to baseline) or in patients with complete response (values of serum creatinine below 1.5 mg/dl, for at least two consecutive days.
In patients showing an incomplete response (decrease of serum creatinine of at least 30 % with respect to the baseline but without reaching a value below 1.5 mg/dl on day 7), treatment with terlipressin may be maintained to a maximum of 14 days.
In most clinical studies supporting the use of terlipressin for the treatment of hepatorenal syndrome, human albumin was administered simultaneously at a dosage of 1 g/kg BW on the first day and afterwards at a dosage of 20 - 40 g/day.
The usual duration of the treatment of hepatorenal syndrome is 7 days, being the maximum duration recommended 14 days.

Terlipressin acetate EVER Pharma should only be used with caution in patients over 70 years, and patients with chronic renal failure.
Type 1 hepatorenal syndrome:
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.

Terlipressin acetate EVER Pharma is not recommended in children and adolescents due to insufficient experience on safety and efficacy.

A dose adjustment is not required in patients with liver failure.
Type 1 hepatorenal syndrome:
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.

Preparation of the injection or infusion

For administration, the required volume should be extracted from the vial with a syringe.

Store in a refrigerator (2˚C-8°C). Do not freeze.
For single use only. Discard any unused solution.