Terlip™

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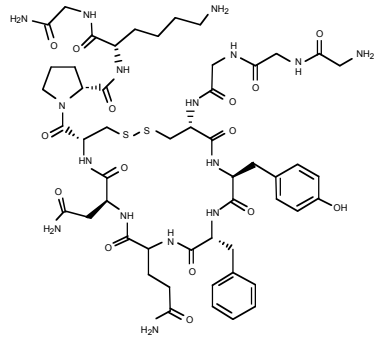
(Terlipressin acetate)

Lyophilized powder for I.V. injection

1mg

DESCRIPTION

TERLIP (Terlipressin acetate) is an analogue of vasopressin and is an inactive prodrug which is slowly converted in the body to lypressin and has the general physiological action of vesopressin. Chemically, terlipressin is 1-{[(4R,7S,10S,13S,16S,19R)-19-[[2-[[2-[(2-aminoacetyl) amino]acetyl}amino)acetyl]amino}-7-(2-amino-2-oxoethyl)-10-(3-amino-3-oxopropyl)-13-benzyl-16-(4-hydroxybenzyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-4-yl]carbonyl}-L-prolyl-N -(2-amino-2-oxoethyl)-L-lysinamide. The molecular formula is $C_{52}H_{74}N_{16}O_{15}S_2$ and the structural formula is:



Terlipressin Acetate

QUALITATIVE & QUANTITATIVE COMPOSITION

TERLIP (Terlipressin acetate) Injection 1mg is available for intravenous administration as:

Terlip injection 1mg
Each vial of lyophilized powder contains:
Terlipressin acetate… 1mg
(equivalent to Terlipressin 0.86mg)

CLINICAL PHARMACOLOGY

Mechanism of Action

Terlipressin acetate may be regarded as a circulating depot of lysine vasopressin. Following intravenous injection, three glycyl moieties are enzymatically cleaved from the N-terminus to release lysine vasopressin. The inactive pre-hormone terlipressin slowly releases bioactive lysine vasopressin.
The slowly released vasopressin reduces blood flow in the splanchnic circulation in a prolonged manner, inhibits portal hypertension with simultaneous reduction of blood circulation in portal vessels. Terlipressin contracts smooth oesophageal muscle with consecutive compression of oesophageal varices, thereby helping to control bleeding from ruptured oesophageal varices.

Pharmacokinetics

The pharmacokinetics follows a two compartment model. The release of lysine-vasopressin is maintained for at least 180 minutes. Due to cleavage of the glycyl groups from terlipressin, lysine vasopressin is slowly released and reaches maximal concentrations after 120 minutes and has duration of activity of 4 to 6 hours. The mean plasma half-life of terlipressin is 24 ± 2minutes. After bolus intravenous injection terlipressin elimination follows second order kinetics. Plasma half-life was calculated as 8 to 12 minutes during the distribution phase (0 to 40 minutes) and 50 to 80 minutes during the elimination phase (40 to 180 minutes). Urine contains only 1% of the injected terlipressin, which indicates almost complete metabolism by endopeptidases and exopeptidases of liver and kidneys.

THERAPEUTIC INDICATIONS

TERLIP (Terlipressin acetate) is indicated in the treatment of bleeding oesophageal varices.

DOSAGE AND ADMINISTRATION

Adults
Initially 1-2 mg terlipressin acetate (corresponding to 1-2 vials of TERLIP) is administered.
Depending on the patient's body weight the dose can be adjusted as follows:

- Weight less than 50kg: 1mg.
- Weight 50kg to 70kg: 1.5mg.
- Weight exceeding 70kg: 2mg.

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

The approximate value for the maximum daily dose of terlipressin acetate is 120 to 150•g/kg body weight. The therapy is to be limited to 2 to 3 days.

TERLIP (Terlipressin acetate) is dissolved with 2mL of 0.9% NaCl solution for injection and is applied intravenously. The intravenous injection should be given during the period of one minute.

ADVERSE REACTIONS

Terlipressin is only recommended for the short-term treatment of bleeding oesophageal varices, so few adverse reactions have been reported.
Following are the adverse reactions reported during terlipressin acetate treatment:

Common: Hyponatraemia, headache, ventricular and supra ventricular arrhythmia, bradycardia, tachycardia, signs of ischemia in the ECG, hypertension, hypotension, peripheral ischemia, cyanosis, abdominal cramps, nausea, diarrhea, paleness.

Uncommon: Triggering of a convulsive disorder, angina pectoris, acute hypertension rise (in particular in patients suffering from hypertension), pain in the chest, bronchiospasm, respiratory arrest, lymphangitis.

Very rare: Hyperglycemia, stroke, myocardial ischemia and infarction, left ventricular failure, dyspnea and local cutaneous necrosis.

CONTRAINDICATIONS

Terlipressin acetate is contraindicated in:

- Patients with known hypersensitivity to the active substances or to any of the excipients.
- Children and adolescents.
- Patients with septic shock.
- Pregnancy as it has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. Terlipressin acetate may have harmful effects on pregnancy and fetus. Information on transfer of terlipressin acetate to breast milk is sufficient. Terlipressin acetate should not be used in breast feeding women.

PRECAUTIONS

- Terlipressin acetate should only be used with caution and under strict monitoring of the patients in the following cases: bronchial asthma, respiratory deficiencies, uncontrolled hypertension, cerebral or peripheral vascular diseases, cardiac arrhythmias, coronary deficiencies or previous myocardial infarction, chronic renal insufficiency.
- Due to the weak antidiuretic effect of terlipressin acetate

(only 3% of the antidiuretic effect of native vasopressin) especially patients with already disturbed electrolyte metabolism should be monitored for a possible hyponatraemia and hypokalaemia.
- Terlipressin acetate should only be used with caution in patients over 70 years.
- Terlipressin acetate should only be used with caution in patients with chronic renal failure.

DRUG INTERACTIONS
- Terlipressin increases the hypotensive effect of non selective •-blockers on the portal vein. Concomitant treatment with drugs known to induce bradycardia (e.g., propofol, sufentanil) can cause severe bradycardia.
- Terlipressin can trigger ventricular arrhythmias including "Torsade de pointes" 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).

OVERDOSAGE
The recommended dose should not be exceeded in any case, since the risk of severe circulatory adverse effects is dose-dependent. An acute hypertensive crisis, especially in patients with recognized hypertension can be controlled with a vasodilator-type alpha-blocker, e.g., 150•g clonidine intravenously. Bradycardia requiring treatment should be treated with atropine.

STORAGE
Store below 20^{o}C (Preferably in a refrigerator). Protect from sunlight & moisture.
Use immediately after reconstitution.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
TERLIP (Terlipressin acetate) Injection 1mg is available as lyophilized powder for injection as one vial along with 2mL 0.9% NaCl solution for injection.

Keep out of reach of children.

To be sold on a prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Hybio Pharmaceuticals Co. Ltd.,
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P.R. China.

Manufactured for:

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