EVERPRESSIN

1. Name of the medicinal product

EVERPRESSIN

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

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. To be taken into consideration by patients on a controlled sodium diet.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

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

4. Clinical particulars

4.1 Therapeutic indications

Everpressin is indicated in for the treatment of:

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

4.2 Posology and method of administration

Posology

Adults

1) Short term management of bleeding oesophageal varices:

The administration of terlipressin serves the emergency care for acute bleeding oesophageal varices until endoscopic therapy is available. Afterwards the administration of terlipressin for the treatment of oesophageal varices is usually an adjuvant therapy to the endoscopic haemostasis.

Initial dose: The recommended initial dose is 1 to 2 mg terlipressin acetate[#] (equivalent to 5 to 10 ml of solution) administered by intravenous injection over a period of time.
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 Everpressin is 120 µg terlipressin acetate per kg body weight.
The therapy is to be limited to 2 – 3 days in adaptation to the course of the disease.
The intravenous injection 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.

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 the 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.

Elderly patients
Everpressin should be used with caution in patients over 70 years of age (see section 4.4).

Paediatric population
Everpressin is not recommended in children and adolescents due to insufficient experience on safety and efficacy (see section 4.4).

Renal insufficiency
Everpressin should only be used with caution in patients with chronic renal failure (see section 4.4).

Hepatic insufficiency
A dose adjustment is not required in patients with liver failure.

Method of administration
For intravenous use only. The solution should be inspected prior to administration. Do not use Everpressin if it contains particles or is discolored.

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

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Pregnancy

4.4 Special warnings and precautions for use

In principle the use of the product should be confined to specialist supervision in units with facilities for regular monitoring of the cardiovascular system, haematology and electrolytes.

Everpressin should only be used with caution and under strict monitoring of the patients in the following cases:
• septic shock
• bronchial asthma, respiratory deficiencies
• uncontrolled hypertension
• cerebral or peripheral vascular diseases
• cardiac arrhythmias
• coronary deficiencies or previous myocardial infarction
• chronic renal insufficiency
• elderly patients over 70 years of age as experience is limited in this group.

Also hypovolaemic patients often react with an increased vasoconstriction and atypical cardiac reactions.

Terlipressin has a weak antidiuretic effect (only 3% of the antidiuretic effect of native vasopressin) therefore patients with a history of disturbed electrolyte metabolism should be monitored for a possible hyponatraemia and hypokalaemia.

lt is advised to monitor the arterial blood pressure, heart rate, serum sodium and potassium and fluid balance continuously.

In emergency situations which require an immediate treatment before sending the patient to a hospital symptoms of hypovolaemia have to be considered.

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.

Terlipressin has no effect on arterial bleeding.

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

Skin Necrosis:
During post-marketing experience several cases of cutaneous ischemia and necrosis unrelated to the injection site (see section 4.8) have been reported. Patients with peripheral venous hypertension or morbid obesity seem to have a greater tendency to this reaction. Therefore, extreme caution should be exercised when administering terlipressin in these patients.

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, electrolytic anormalities, concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that can cause hypokalaemia or hypomagnesemia (e.g. some diuretics) (see section 4.5).

Special populations
Particular caution should be exercised in the treatment of children, adolescents and elderly patients, as experience is limited and there are no safety and efficacy data available regarding dosage recommendation in this population.

This medicinal product contains 0.8 mmol (or 18.4 mg) sodium per 5 ml dose and 1.6 mmol (or 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

Terlipressin increases the hypotensive effect of non-selective β-blockers on the portal vein. The reduction in heart rate and cardiac output caused by the treatment can be attributed to the inhibition of the reflexogenic activity of the heart through the vagus nerve as a result of increased blood pressure. 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" (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
Everpressin is contraindicated during pregnancy as 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 has been shown in rabbits after treatment with terlipressin (see section 5.3).

Breastfeeding
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 breastfed child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from terlipressin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Rare	not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			hyponatraemia	hyperglycaemia	
Nervous system disorders		headache	triggering of a convulsive disorder	stroke	
Cardiac disorders		ventricular and supra-ventricular arrhythmia, bradycardia, signs of ischaemia in the ECG	angina pectoris, acute hypertension rise, in particular in patients already suffering from hypertension (generally, it decreases spontaneously), atrial fibrillation, ventricular extrasystoles, tachycardia, chest pain, myocardial infarction, fluid overload with pulmonary oedema	myocardial ischemia	cardiac failure, Torsade de Pointes
Vascular disorders		hypertension, hypotension, peripheral ischaemia, peripheral	intestinal ischaemia, peripheral cyanosis, hot flushes		

		vasoconstriction, facial pallor			
Respiratory, thoracic and mediastinal disorders			pain in the chest, bronchospasm, respiratory distress, respiratory failure	dyspnoea	
Gastrointestinal disorders		transient abdominal cramps, transient diarrhoea	transient nausea, transient vomiting		
Skin and subcutaneous tissue disorders		paleness	lymphangitis		skin necrosis unrelated to the site of administration
Reproductive system and breast disorders		abdominal cramps (in women)			
Pregnancy, puerperium and perinatal conditions					uterine constriction, decreased uterine blood flow
General disorders and administration site conditions				local cutaneous necrosis	

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including "Torsade de pointes" have been reported (see sections 4.4 and 4.5).

During post-marketing experience, several cases of cutaneous ischemia and necrosis unrelated to the injection site have been reported (see section 4.4).

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 the Health Product Pharmacovigilance Center at: http://thaihpvc.fda.moph.go.th.

4.9 Overdose

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 microgram clonidine intravenously.

Bradycardia requiring treatment should be treated with atropine.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic hormonal preparations, posterior pituitary lobe hormones, vasopressin and analogues, ATC code: H01BA04

Terlipressin inhibits portal hypertension with simultaneous reduction of blood circulation in portal vessels. Terlipressin contracts smooth oesophageal muscle with consecutive compression of oesophageal varices.

The inactive pre-hormone terlipressin slowly releases bioactive lysine-vasopressin. Metabolic elimination takes place concomitantly and within a period of 4-6 hours. Therefore, concentrations remain continuously above the minimal effective dose and below toxic concentrations.

Specific effects of terlipressin are assessed as follows:

Gastrointestinal system:
Terlipressin increases the tone of vascular and extravascular smooth muscle cells. The increase in arterial vascular resistance leads to decrease of splanchnic hypervolemia. The decrease of the arterial blood supply leads to reduction of pressure in the portal circulation. Intestinal muscles contract concomitantly which increases intestinal motility. The muscular wall of the oesophagus also contracts which leads to closure of experimentally induced varices.

Kidneys:
Terlipressin has only 3% antidiuretic effect of the native vasopressin. This residual activity is of no clinical significance. Renal blood circulation is not significantly effected in normovolemic condition. Renal blood circulation is increased, however, under hypovolemic condition.

Blood pressure:
Terlipressin induces a slow haemodynamic effect which lasts 2-4 hours. Systolic and diastolic blood pressure increase mildly. More intense blood pressure increase has been observed in patients with renal hypertension and general blood vessel sclerosis.

Heart:
All studies reported that no cardio-toxic effects were observed, not even under the highest dose of terlipressin. Influences on the heart, such as bradycardia, arrhythmia, coronary insufficiency, occur possibly because of reflex or direct vascular constrictive effects of terlipressin.

Uterus:
Terlipressin causes significant decrease in myometrial and endometric blood flow.

Skin:
The vasoconstrictive effect of terlipressin causes significant decrease in blood circulation of the skin. All studies reported obvious paleness on face and body.

In conclusion, the main pharmacological properties of terlipressin are its haemodynamic effects and its effects on smooth muscle. The centralization effect under hypovolemic condition is a desired side effect in patients with bleeding oesophageal varices.

5.2 Pharmacokinetic properties

After bolus intravenous injection terlipressin elimination follows second order kinetics. Plasma half-life was calculated as 8-12 minutes during the distribution phase (0-40 minutes) and 50-80 minutes during the elimination phase (40-180 minutes). 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. Urine contains only 1% of the injected terlipressin, which indicates almost complete metabolism by endo- and exopeptidases of liver and kidneys.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single- and repeat-dose toxicity, and genotoxicity. No carcinogenicity studies have been performed with terlipressin.

At doses relevant to humans, the only effects observed in animals were those attributed to the pharmacological activity of terlipressin.

Adverse reactions observed in animal studies with possible relevance to clinical use were as follows:

Due to its pharmacological effect on smooth muscles terlipressin may induce abortion in the first trimester.

An embryo-fetal study in rats demonstrated no adverse effects of terlipressin. In rabbits abortions occurred, probably related to maternal toxicity, and there were ossification anomalies in a small number of fetuses and a single isolated case of cleft palate.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride
Acetic acid
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
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

Unopened: 36 months
Once the vial has been opened, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
Store in the vial in the outer carton.

6.5 Nature and contents of container

Colourless glass vials, closed with bromobutyl rubber stopper and sealed with aluminium flip-off cap.
Each vial contains 5 ml or 10 ml of solution.
Pack sizes: 1 x 5 ml, 5 x 5 ml, 1 x 10 ml, 5 x 10 ml

6.6 Special precautions for disposal and other handling

For single use only.
No special requirements.
Discard any unused solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

American Taiwan Biopharm Co., Ltd.
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8. Marketing authorisation number
1C 150xx/64 (NG)

9. Date of first authorisation/renewal of the authorisation
DD/MM/2021

10. Date of revision of the text
15/11/2021