TERLIPRESSIN EVER PHARMA Solution for Injection

NAME OF THE MEDICINE

Terlipressin (as terlipressin acetate).

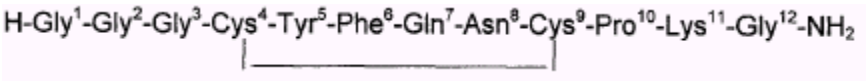
The chemical name is *N*-[*N*-(*N*-Glycylglycyl) glycyl]-8-L-lysinevasopressin.

Terlipressin has an empirical formula of $C_{52}H_{74}N_{16}O_{15}S_2$ and a molecular weight of 1227.4.

CAS No: 14636-12-5. The pKa is approximately 10.

Terlipressin is freely soluble in water. Although the active ingredient is terlipressin, the drug substance included in this product contains non-stoichiometric amounts of acetic acid and water, and this material is freely soluble in water.

The structural formula of terlipressin is



DESCRIPTION

TERLIPRESSIN EVER PHARMA solution for injection is for intravenous injection.

The drug product TERLIPRESSIN EVER PHARMA contains 0.17 mg/mL terlipressin (anhydrous, acetate free, equivalent to 0.2 mg/mL terlipressin acetate) and is a clear colourless aqueous sterile solution for injection.

The following presentations are available:
0.85 mg/5 mL solution for injection (Terlipressin, anhydrous and acetate free)
1.7 mg/10 mL solution for injection (Terlipressin, anhydrous and acetate free)

List of excipients

TERLIPRESSIN EVER PHARMA solution for injection contains the following excipients:
Sodium chloride, acetic acid, sodium hydroxide, hydrochloric acid, water for injections.

PHARMACOLOGY

Pharmacodynamics

Terlipressin belongs to the pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues), ATC code: H01B A04.

Terlipressin is a dodecapeptide that has three glycyl residues attached to the N-terminal of lysine vasopressin (LVP). Terlipressin acts as a pro-drug and is converted via enzymatic cleavage of its three glycyl residues to the biologically active lysine vasopressin. A large body of evidence has consistently shown that terlipressin given at doses of 0.85 mg and 1.7 mg respectively (equivalent to terlipressin acetate 1 mg and 2 mg respectively) can effectively reduce the portal venous pressure and produces 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 1.7 mg terlipressin (2 mg terlipressin acetate) is more effective than 0.85 mg (1 mg terlipressin acetate), as the higher dose produces a dependable effect throughout the period of treatment (4 hours).

The primary pharmacodynamic effects of terlipressin are the vasoconstrictive effects mediated through V_{1a} receptors on vascular smooth muscle in the splanchnic and portal circulation. Moreover, terlipressin can also act via V_{1a} receptors to increase systemic mean arterial pressure and cause a reflexogenic heart rate reduction. Regarding secondary pharmacodynamic effects, terlipressin has shown minimal effects on the fibrinolytic system in cirrhotic patients acting on V_2 receptors. V_2 mediated antidiuretic effects have been observed with terlipressin corresponding to 3% of the native vasopressin. No consistent effect on serum sodium has been seen in healthy volunteers but there may be a potential risk for hyponatremia associated with terlipressin when treating patients with portal hypertension and actively bleeding oesophageal varices. No influence of V_{1b} receptors has been observed as illustrated by no significant effects observed on adrenocorticotropic hormone and cortisol release.

Pharmacokinetics

The pharmacokinetic properties of terlipressin have been investigated in healthy volunteers and in cirrhotic patients, with similar PK characteristics observed in both populations. The intravenous pharmacokinetic profile can be described using a two-compartment model with a distribution and elimination half-life of approximately 8 and 40 minutes, respectively. The kinetics of terlipressin is linear with a plasma clearance of about 9 mL/kg/min and a volume of distribution of 0.5 L/kg.

The estimated concentrations of lysine-vasopressin show an initial appearance in plasma 30 minutes after administration of terlipressin with a peak concentration occurring between 60 and 120 minutes. Terlipressin has also been found to be distributed to ascitic fluid, reaching equilibrium with plasma after 60 min.

About 1 % of the dose administered was excreted unchanged in the urine which indicates almost complete metabolism by peptidases.

Because of a 100% cross-reactivity there is no available RIA-method to differentiate terlipressin from lysine-vasopressin.

CLINICAL TRIALS

Bleeding Oesophageal Varices (BOV)

The data evaluated for this indication were from a literature-based submission which uncovered 28 efficacy publications, including 8 that were published since the 2003 Cochrane Review. Several pharmacokinetic and dose ranging studies were also provided. Twenty-two other publications as well as post-marketing reports and a 1991 paper on post-marketing experience, and 127 literature references were also included.

The studies that contribute the most to demonstrating the efficacy of terlipressin in bleeding oesophageal varices are four pivotal, placebo-controlled studies (Walker et al, 1986; Freeman et al, 1989; Söderlund et al, 1990; Levacher et al, 1995) and two supportive, controlled studies involving endoscopic treatment (Escorsell et al 2000; Abid et al, 2009). Several other controlled studies provide further supportive evidence. In both the pivotal and supporting studies there was a consistently high rate of bleeding control with terlipressin, despite substantial differences in study design, the dose used and assessment of treatment effect. All doses in the clinical trials section below are stated as 1 mg or 2 mg terlipressin to mean 1 mg or 2 mg terlipressin acetate.

Placebo-controlled studies

The study of Walker *et al*. (1986) was a randomised, double-blind, placebo-controlled study of terlipressin as an addition to standard therapy, in cirrhotic patients with endoscopically verified variceal bleeding. After endoscopy, patients were randomised to treatment with either an initial 2 mg i.v. injection of terlipressin, followed by a 1 mg injection every 4 h for a total of 36 h of treatment, or to corresponding placebo. A total of 50 bleeding episodes in 34 patients were randomised; all re-randomised patients had been discharged between randomisations.

The primary efficacy endpoint of control of bleeding within 36 h was met in 25/25 (100%) of the episodes randomised to terlipressin, compared to 20/25 (80%) of the episodes randomised to placebo ($p < 0.05$). A total of 5/25 (20%) of the episodes randomised to terlipressin were considered treatment failures (including episodes requiring balloon tamponade or sclerotherapy), in contrast to 12/25 (48%) episodes randomised to placebo ($p < 0.05$). There were no statistically significant differences between the treatment groups in the secondary endpoints of blood and plasma transfusion requirements, duration of bleeding, rebleeding after 36 h of treatment, or in-hospital mortality (terlipressin: 3 deaths/25 episodes, 12%; placebo: 8 deaths/25 episodes, 32%, n.s.).

The study of Freeman *et al*. (1989) was a randomised, double-blind, placebo-controlled study of terlipressin in patients with portal hypertension and endoscopically verified variceal bleeding. After endoscopy, patients were randomised to treatment with either an initial 2 mg i.v. injection of terlipressin, followed by a 2 mg injection every 4 h for a total of 24 h of treatment (or at least 8 h after the bleeding stopped), then a 1 mg injection every 4 h for an additional 16 h; or to corresponding placebo. A total of 31 bleeding episodes in 29 patients were randomised.

The primary efficacy endpoint of initial control of bleeding without the need for balloon tamponade/rescue sclerotherapy was met in 9/15 (60%) of the episodes randomised to terlipressin, compared to 6/16 (37%) of the episodes randomised to placebo (n.s.). During follow-up, 1 patient in the terlipressin group and 3 patients in the placebo group had rebleedings (all were successfully controlled by rescue sclerotherapy), leaving 8/15 (53%) of the episodes randomised to terlipressin and 3/16 (19%) of the episodes randomised to placebo as being successfully controlled at 5 days (secondary endpoint; $p < 0.05$). There were no statistically significant differences between the treatment groups in the further secondary endpoints of blood transfusion requirement or in-hospital mortality (terlipressin: 3 deaths/15 episodes, 20%; placebo: 4 deaths/16 episodes, 25%).

The study of Söderlund *et al*. (1990) was a randomised, double-blind, placebo-controlled study of terlipressin in cirrhotic patients with endoscopically verified variceal bleeding. After endoscopy, patients were randomised to treatment with either an initial 2 mg i.v. injection of terlipressin, followed by a 2 mg injection every 4 h for a total of 24 to 36 h of treatment, or to corresponding placebo. Treatment was discontinued with a control endoscopy (including sclerotherapy) between 24 and 36 h after the initiation of treatment, or until emergency intervention (e.g. balloon tamponade) was required. A total of 60 patients were randomised; no patient was randomised more than once.

The primary efficacy endpoint of initial control of bleeding without emergency intervention ('success') was met in 28/31 (90%) of the patients randomised to terlipressin, and in 17/29 (59%) of the patients randomised to placebo ($p=0.0067$; Fisher's exact test). During treatment, 2 patients in the terlipressin group and 1 patient in the placebo group had rebleedings, thus the secondary endpoint of 'efficacy' (defined as absence of blood in two consecutive gastric rinses, and no ongoing bleeding/fresh blood at control endoscopy) was met in 26/31 (84%) of the patients in the terlipressin group and in 16/29 (55%) of the patients in the placebo group ($p=0.024$; Fisher's exact test). During treatment, transfusion requirements were statistically significantly lower in the terlipressin group than in the placebo group. During the whole study, from first injection to 24-hour follow-up, 22/31 (71%) of the patients in the terlipressin group and 28/29 (97%) of the patients in the placebo group required any blood transfusion ($p < 0.05$). In-hospital mortality was 3/31 (10%) of the patients in the terlipressin group and 11/29 (38%) of the patients in the placebo group ($p < 0.05$).

The study of Levacher *et al*. (1995) was a randomised, double-blind, placebo-controlled study of the combination of terlipressin and nitroglycerin, in cirrhotic patients with upper GI bleeding as diagnosed by gastric lavage. Patients were randomised by an emergency team in the home setting, to treatment with either terlipressin (an initial injection of 1 mg for patients <50 kg, 1.5 mg for patients 50-70 kg, or 2 mg for patients >70 kg; patients received repeat injections at 4 h and 8 h) and a transdermal nitroglycerin patch (24 mg/12 h), or to corresponding placebo injections and excipient patch. After initiation of treatment, patients were transferred to the hospital intensive care unit. Concurrent treatments in both treatment groups included endoscopic sclerotherapy, but this was not necessarily performed before the primary efficacy evaluation (control of bleeding at 12 h).

A total of 85 bleeding episodes in 77 patients were randomised; all re-randomised patients had at least 30 days between bleeding episodes. One patient had been included by 'error', therefore the analysis was performed on 84 bleeding episodes in 76 patients.

The primary efficacy endpoint of control of bleeding (without rebleeding) at 12 h was met in 29/41 (71%) of the episodes randomised to terlipressin, and in 20/43 (47%) of the episodes randomised to placebo ($p < 0.05$). There was no statistically significant difference between the treatment groups in the secondary endpoint of frequency of rebleeding after 12 h; however, the episodes randomised to terlipressin required fewer blood transfusions than episodes randomised to placebo (a mean of versus 1.9 units/day; $p < 0.05$). Mortality was lower in the episodes randomised to terlipressin than in those randomised to placebo at 15 days (8/41, 20% *vs*. 18/43, 42%; $p < 0.05$) but not at 42 days (12/41, 36% vs. 20/43, 47%; n.s.). When adjusting for Child-Pugh class, the difference in mortality was statistically significant in favour of terlipressin also at 42 days; in all episodes not classified as Child-Pugh C, the patient survived.

Study versus endoscopic treatment

The study of Escorsell *et al*. (2000) was a randomised, non-blinded study of terlipressin versus endoscopic sclerotherapy in cirrhotic patients with endoscopically verified bleeding oesophageal varices. During diagnostic endoscopy, patients were randomised to treatment with either terlipressin (initial 2 mg i.v. injection followed by 2 mg injections every 4 h for 48 h or until control of bleeding was achieved, followed by 1 mg injections every 4 h for 5 more days) or endoscopic sclerotherapy (one immediate intra-paravariceal injection of 5% ethanolamine or 1% polidocanol; no further sclerotherapy until at least one study endpoint was reached). A total of 219 patients were randomised; no patient was randomised more than once.

The primary efficacy endpoint of initial control of bleeding within 48 h was met in 85/105 (81%) patients randomised to terlipressin and in 94/114 (82%) of the patients randomised to sclerotherapy (n.s.). The secondary endpoint of early rebleeding (within 5 days) occurred in 15 patients (14%) in the terlipressin group and in 16 patients (14%) in the sclerotherapy group (n.s.). There were no statistically significant differences between the treatment groups in transfusion requirements, length of hospitalisation (including ICU stay), need for alternative therapy, or the frequency of late rebleeding (terlipressin, 26/105 patients, 25%; sclerotherapy, 29/114 patients, 25%). The 42-day mortality rates were similar between treatment groups (terlipressin, 29/105 patients, 28%; sclerotherapy, 19/114 patients, 17%; n.s).

Study versus active comparator, in addition to endoscopic treatment

The study of Abid *et al*. (2009) was a randomised, double-blind non-inferiority study of terlipressin or octreotide as additions to endoscopic banding ligation, in cirrhotic patients with endoscopically verified oesophageal variceal bleeding. On admission but before diagnostic endoscopy, patients were randomised to treatment with either terlipressin (initial 2 mg i.v. injection followed by 1 mg injections every 6 h for a total of 72 h of treatment) or with octreotide (initial 100 μg i.v. injection and 50 μg/h infusion for a total of 72 h); both treatment groups received mock placebo treatments. All patients had endoscopic banding ligation within 24 h. A total of 359 patients were randomised before diagnostic endoscopy. Of these patients, 35 were excluded from analysis due to violation of inclusion/exclusion criteria. Thus, 324 patients with endoscopically confirmed oesophageal variceal bleeding were included in the ITT analysis.

The primary efficacy endpoint of control of bleeding (according to Baveno III criteria) within 72 h was met in 158/163 (97%) of the patients randomised to terlipressin + banding ligation, and in 160/161 (99%) of the patients randomised to octreotide + banding ligation (n.s.). Based on a prespecified non-inferiority margin of 11% for the lower limit of the 95% confidence interval, it was concluded that terlipressin + banding ligation was non-inferior to octreotide + banding ligation. The mean length of hospitalisation was shorter in the terlipressin group than in the octreotide group (108 h vs. 126 h, $p < 0.001$). In-hospital mortality was 9/163 (6%) in the terlipressin group and 7/161 (4%) in the octreotide group (n.s.).

Duration of treatment

In the placebo-controlled studies, treatment duration up to the primary efficacy endpoint varied between 12 h and 36 h. The maximum duration of treatment with 2 mg doses (given either every 4 hours or every 6 hours) in any of the evaluated studies was 48 hours (see DOSAGE AND ADMINISTRATION). In those studies where treatment was continued for up to 5 days, a 1 mg dose was used for some or all of the dosing period. A consensus statement from the fifth Baveno Congress (Baveno V) recommends treatment for up to 5 days.

Hepatorenal Syndrome (HRS)

The efficacy and safety of terlipressin to improve renal function in patients with hepatorenal syndrome type 1 was assessed in one published pivotal study (Sanyal et al. 2008; also known as OT-0401 and NCT00089570) and was supported by another published study (Martín-Llahí et al. 2008; also known as TAHRS and NCT00287664).

Study NCT00089570:

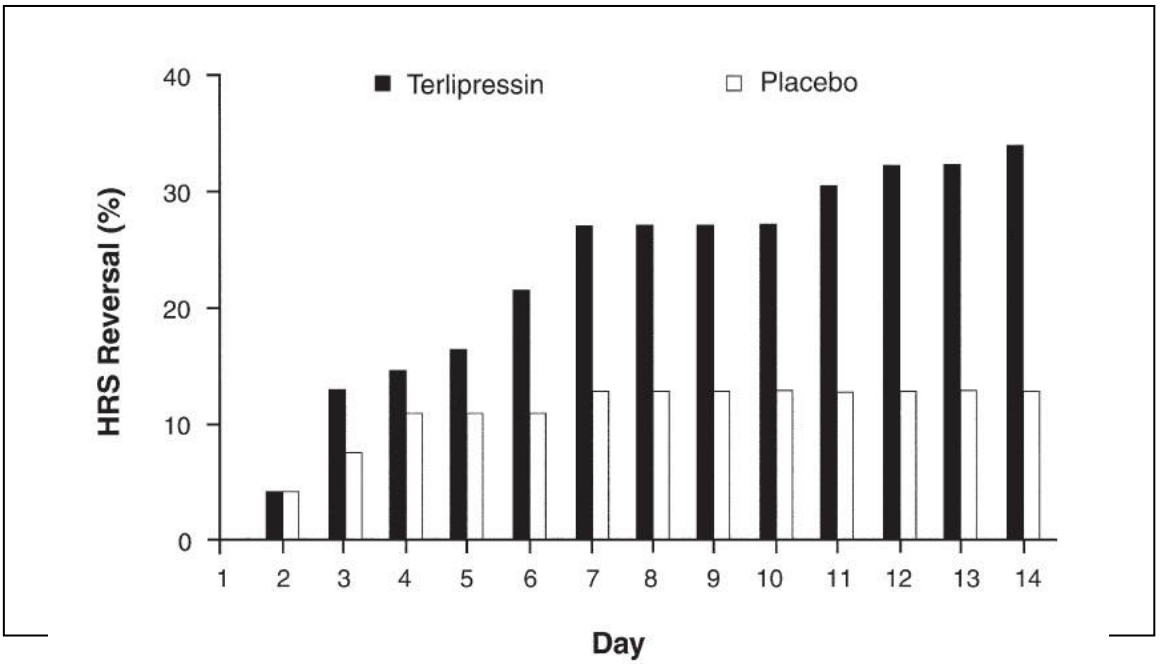
The study of Sanyal *et al.* (2008) was a prospective, randomised, double-blind, placebo-controlled multicentre, phase III study in 112 HRS type 1 patients who were randomised in a 1:1 ratio to receive either intravenous terlipressin via slow intravenous push at an initial dose of 0.85 mg (as 1 mg terlipressin acetate) every 6 hours or matching placebo for a period of up to 14 days. Dose was increased to 1.7 mg every 6 hours (as 2 mg terlipressin acetate) if serum creatinine had not decreased by at least 30% of baseline value. Equal numbers of patients (88%) in both groups also received intravenous albumin for plasma volume expansion. The mean patient age was 51.7 years, 71.4% were male, 89% were Caucasian. The primary causes of cirrhosis were alcohol (52%) and hepatitis C (37%). Other relevant baseline parameters were (mean): Child-Pugh score 11.5, MELD score 33.4, serum creatinine 3.91 mg/dL [345.6 µmol/L], total bilirubin 15.4 mg/dL [263.3 µmol/L].

Patients were monitored for up to 180 days. The primary endpoint was treatment success at day 14 (defined as serum creatinine (SCr) level ≤ 1.5 mg/dL [132.6 µmol/L] on 2 occasions at least 48 hr apart, without dialysis, death, or recurrence of HRS type 1 on or prior to day 14). The secondary endpoints included change in SCr level from baseline to day 14; HRS reversal (defined as SCr level ≤ 1.5 mg/dL [132.6 µmol/L] during treatment without dialysis); and survival up to 180 days. Treatment outcomes are shown in the Table 1, cumulative incidence of HRS reversal in Figure 1.

Table 1. Treatment Outcomes

	Terlipressin n (%)	**Placebo n (%)**	***P* value**
All patients	(n = 56)	(n = 56)	
Treatment success at day 14	14 (25.0)	7 (12.5)	0.093
HRS reversal	19 (33.9)	7 (12.5)	0.008
Patients who received 3 days of treatment	(n = 36)	(n = 39)	
Treatment success at day 14	14 (38.9)	7 (17.9)	0.046
HRS reversal	19 (52.8)	7 (17.9)	0.002

Figure 1. Cumulative Incidence of HRS Reversal by Day
(Treatment began on day 1)



***Survival*:** Overall survival at day 180 was not significantly different between the terlipressin (n = 24/56; 43%) and placebo (n = 21/56; 38%) groups (*P* = 0.839, see Figure 2). Transplant-free survival up to day 180 was also similar in both groups (7/56; 13% for terlipressin vs. 5/56; 9% for placebo). Analysis of overall survival and transplant-free survival for HRS reversal responders vs. non-responders in each treatment group showed a separation in both survival distributions among responders and non-responders. Patients achieving HRS reversal irrespective of treatment, exhibited significantly longer rates of overall survival to day 90 (p = 0.025) and day 180 (p = 0.0073) (Figure 3).

Figure 2. Kaplan-Meier plot of overall survival up to day 180
Observations were censored at the last time a patient was known to be alive (represented by open circles).

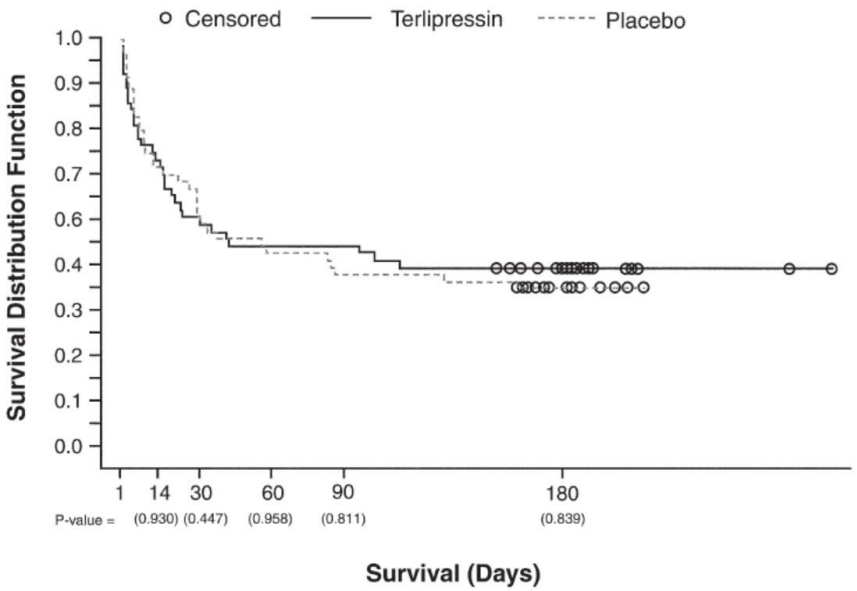
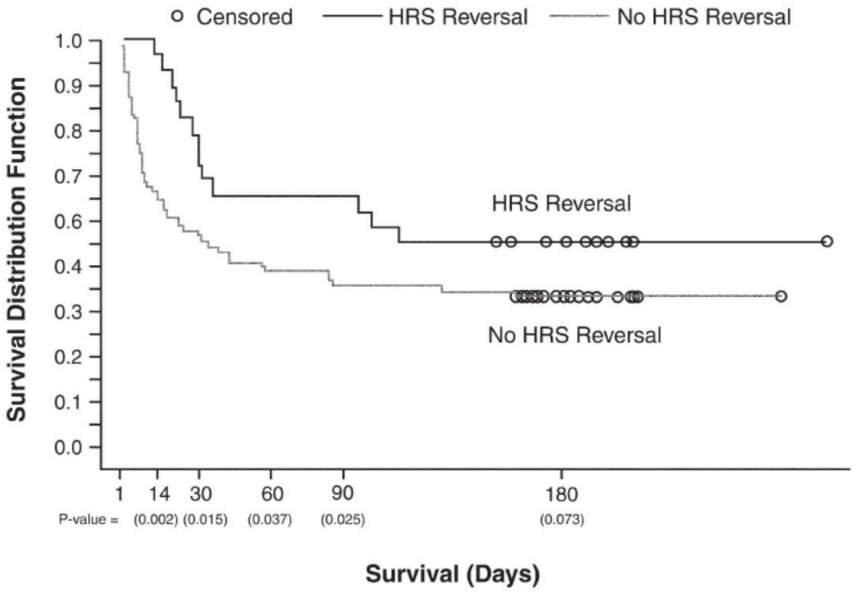


Figure 3. Overall survival for HRS reversal vs no HRS reversal Observations were censored at the last time a patient was known to be alive (represented by *open circles*). All patients are included irrespective of treatment.



Study NCT00287664 (TAHRS)

The study of Martín–Llahí *et al.* (2008) was a supportive open-label, comparative multicentre study in 46 patients who were randomised in a 1:1 ratio to receive either intravenous terlipressin (0.85 – 1.7 mg (as 1 to 2 mg terlipressin acetate) every 4 hours) plus 20% albumin or 20% albumin alone, for a maximum of 15 days. The majority of patients had HRS type 1 (35/46) and the remainder, HRS type 2 (11/46).

The study was terminated prematurely following a protocol specified interim futility analysis of survival and insufficient enrolment. Findings of renal function improvement were consistent with those in the pivotal study of Sanyal *et al* (2008). There were no significant differences in survival between the two groups, and the causes of death were also similar in both groups.

INDICATIONS

TERLIPRESSIN EVER PHARMA solution for injection is indicated for the:

- treatment of bleeding oesophageal varices;
- treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for liver transplant.

CONTRAINDICATIONS

Pregnancy.

Hypersensitivity to terlipressin or any other excipients of the product.

PRECAUTIONS

Cardiovascular Effects

Terlipressin should only be used with caution and under strict monitoring of the patients in the following cases:

- uncontrolled hypertension

- cerebral or peripheral vascular diseases
- cardiac arrhythmias
- coronary artery disease or previous myocardial infarction

Terlipressin should not be used in patients with unstable angina or recent acute myocardial infarction.

During post-marketing experience, cases of QT interval prolongation and ventricular arrhythmias including "Torsade de pointes" have been reported. In most cases, patients had predisposing factors such as basal prolongation of the QT interval, electrolyte abnormalities (hypokalaemia, hypomagnesaemia) 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 abnormalities, 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 hypomagnesaemia (e.g. some diuretics) (see INTERACTION WITH OTHER MEDICINES).

Ischaemic Events

To avoid local necrosis the injection must be administered intravenously.

During post-marketing experience several cases of cutaneous ischemia and necrosis unrelated to the injection site 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.

Respiratory Effects

Terlipressin may cause smooth muscle constriction and should be used with caution and under strict monitoring in patients with severe asthma or chronic obstructive pulmonary disease (COPD).

Laboratory Monitoring

During treatment with terlipressin serum creatinine should be monitored at least daily as terlipressin should be used with caution in patients with renal insufficiency.

Fluid balance and electrolytes should be monitored carefully as hyponatraemia, hypokalaemia, hypomagnesaemia and other electrolyte disturbances have been reported.

Children and the Elderly

Because of limited experience, special precaution should be taken during treatment of children and elderly patients. No data are available regarding dosage recommendation in these special patient categories.

Renal Impairment

As data are limited terlipressin should be used with caution and under strict monitoring of the patients in renal impairment.

Effects on fertility

There are no human data on the effects of terlipressin on male or female fertility. In a rat fertility study, mating of terlipressin-treated males (3 weeks prior to mating at 1.8 and 3.6 mg/m^2/day i.v.; ca. 25-50% of the Maximum Recommended Daily Human Dose) with untreated females had no effect on the number of matings and frequency of insemination but led to decreased litter size. In a separate study, testicular atrophy and disturbances of spermiogenesis were observed in male rats treated with terlipressin for 3 weeks at 3.6 mg/m^2/day i.v. Based on animal studies, there is some risk of reduced

fertility in persons taking terlipressin.

Use in Pregnancy (Category D)

Treatment with terlipressin is contraindicated in pregnancy.

Terlipressin is known to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow in humans. Terlipressin may have harmful effects on the pregnancy and the fetus.

Spontaneous abortion and fetal malformations were observed in pregnant rabbits treated with terlipressin throughout organogenesis at i.v. doses (based on body surface area) less than the maximum recommended human daily dose.

Use in Lactation

There are no human or animal data on the excretion of terlipressin into milk or on the safety of terlipressin in infants. Hence, terlipressin should not be used in women who are breast- feeding.

Genotoxicity

Assays for gene mutation and chromosomal damage did not provide any evidence of a genotoxic potential for terlipressin.

Carcinogenicity

Carcinogenicity studies have not been performed.

INTERACTION WITH OTHER MEDICINES

Terlipressin increases the hypotensive effect of non-selective β-blockers on the portal vein. Concomitant treatment with drugs which are known to induce bradycardia (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 elevated blood pressure.

Terlipressin can trigger ventricular arrhythmias including "Torsade de pointes" (see PRECAUTIONS and ADVERSE EFFECTS). 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).

ADVERSE EFFECTS

The reporting of safety data rely on published literature and post marketing surveillance.

Clinical Trials

Three studies assessed safety as primary outcome in totally 1341 patients.

Caletti 1991, a prospective, uncontrolled observational study, enrolled 1258 patients. 21% of the patients experienced a side-effect. The side-effects reported were consistent with the known pharmacological actions of terlipressin.

Bruha 2009, a randomised, double-blind study enrolled 25 patients that were randomised to either 5-day or 10- day treatment. Serum sodium and serum creatinine decreased in both arms during treatment, but rose again after discontinuation of treatment.

Solà 2010, a retrospective cohort study, included 58 patients. Over a 5 day treatment period 67% of the patients developed acute reduction in serum sodium. The hyponatraemia was found to develop rapidly after start of therapy, but was usually reversible with a median recovery time of 4 days after discontinuation of terlipressin.

Post-marketing Experience

The most commonly reported affected system organ classes were: cardiac disorders (66 reactions); vascular disorders (50 reactions); skin and subcutaneous tissue disorders (34 reactions); gastrointestinal disorders (30 reactions); metabolism and nutrition disorders (26 reactions) and nervous system disorders (22 reactions). The table below lists the adverse effects reported for terlipressin in the post-marketing period.

MedDRA System organ class Disorder	**Common (≥1% & <10%)**	**Uncommon (≥0.1% & <1%)**	**Rare (≥0.01% & <0.1%)**	**Not known (cannot be estimated from the available data**
METABOLISM		Hyponatraemia if fluid not monitored;		
NERVOUS SYSTEM	Headache;			
CARDIAC	Bradycardia;	Atrial Fibrillation; Ventricular Extrasystoles; Tachycardia; Chest pain; Myocardial Infarction; Fluid overload with pulmonary oedema;	Ventricular fibrillation;	Torsade de pointes; Cardiac failure;
VASCULAR	Peripheral vasoconstriction; Peripheral ischemia; 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; Decreased uterine blood flow;		
GENERAL		Injection site necrosis;		

During post-marketing experience several cases of cutaneous ischemia and necrosis unrelated to the injection site have been reported.

DOSAGE AND ADMINISTRATION

TERLIPRESSIN EVER PHARMA solution for injection must only be administered intravenously.

Terlipressin 1.7 mg/10 mL solution for injection vial is intended for the administration of a 1.7 mg dose only.

Product is for single use in one patient only. Discard any unused solution.

Bleeding Oesophageal Varices (BOV)

Adults:

Initially an i.v. injection of 1.7 mg terlipressin (2 mg terlipressin acetate, equivalent to 10 mL of solution) is given every 4 hours. When the bleeding is under control the dose can be adjusted to 0.85 mg terlipressin (1 mg terlipressin acetate, equivalent to 5 mL of solution) i.v. every 4 hours. After the initial dose, the dose can also be adjusted to 0.85 mg (1 mg terlipressin acetate [5 mL]) i.v. every 4 hours in patients with body weight < 50 kg or if adverse effects occur. The treatment should not continue for more than 48 hours in total.

Children and Elderly:

No data are available regarding dosage recommendations in these patient populations.

Hepatorenal Syndrome (HRS)

0.85 mg terlipressin (5 mL solution) every 6 hours by slow intravenous bolus injection for 7 to 14 days (administered in association with albumin 20% 100 mL i.v. twice daily for 7 to 14 days).

If serum creatinine (SCr) has not decreased by at least 30% from the baseline value after 3 days, the dose can be increased to a maximum of 1.7 mg terlipressin (10 mL solution) every 6 hours.

It is however recommended that the dose not be increased in patients with severe pre-existing cardiovascular disease or in the presence of an ongoing significant adverse event e.g. pulmonary oedema, ischaemia (see PRECAUTIONS). Treatment should be continued until about 2 days after the patient achieves HRS reversal (SCr less than or equal to 132.6 µmol/L), or be discontinued if the patient undergoes dialysis or liver transplant or if SCr remains at or above baseline after 7 days of treatment.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction. When the patient's symptoms resolve, TERLIPRESSIN EVER PHARMA may be re-commenced at a lower dose or at a less frequent dosing interval (e.g., every 8 – 12 hours). Lowest doses used in the clinical studies ranged from 1.7 to 2.55 mg terlipressin/day. The maximum dose studied (TAHRS Study) was 1.7 mg terlipressin every 4 hours.

OVERDOSAGE

The recommended dose of 1.7 mg (equivalent to 2 mg 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 150 mcg clonidine i.v.

Bradycardia requiring treatment should be treated with atropine.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

TERLIPRESSIN EVER PHARMA solution for injection, vial:

Terlipressin is a clear colourless aqueous sterile solution for injection.

The following presentations are available:

0.85 mg/5 mL solution for injection and 1.7 mg/10 mL solution for injection.

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.

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 – AUST R 288142

1 x 10 mL, 5 x 10 mL – AUST R 288156

Storage conditions

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in the outer carton to protect from light.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

16 August 2018