AUSTRALIAN PRODUCT INFORMATION - GLYPRESSIN® (terlipressin) Solution for Injection

1. NAME OF THE MEDICINE

Terlipressin (as terlipressin acetate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of GLYPRESSIN contains 0.85 mg terlipressin in 8.5 mL of solution.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Solution for Injection. Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

GLYPRESSIN is indicated for the:

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

GLYPRESSIN is administered by intravenous (IV) injection.

Bleeding oesophageal varices: IV injection

Type I hepatorenal syndrome (HRS): IV injection or IV infusion.

Bleeding Oesophageal Varices (BOV)

Adults:

Initially an IV injection of 1.7 mg terlipressin is given every 4 hours. When the bleeding is under control the dose can be adjusted to 0.85 mg terlipressin IV every 4 hours. After the initial dose, the dose can also be adjusted to 0.85 mg IV 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.

Type 1 Hepatorenal Syndrome (HRS)
A slow intravenous bolus injection of 0.85 mg terlipressin every 6 hours for 7 to 14 days. Data indicates that adding human albumin may be more efficacious than treating with terlipressin alone in patients with type 1 hepatorenal syndrome. The dosing of human albumin should be in accordance with current guideline.

If serum creatinine (SCr) has not decreased by at least 30 % from the baseline value after 2 days, the dose can be increased to a maximum of 1.7 mg terlipressin 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 Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Treatment should be maintained until about 2 days after the patient achieves HRS reversal (SCr levels less than or equal to 132.6 micromoles/L). Treatment should be discontinued if the patient undergoes dialysis or liver transplantation, if the patient exhibits a partial response (i.e. SCr level does not decrease below 132.6 micromoles/L) or if the patient exhibits no response (i.e. no reduction of SCr levels), within 14 days of treatment.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction. When the patient's symptoms resolve, GLYPRESSIN 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.

As an alternative to bolus injection terlipressin can be administered as a continuous IV infusion with a starting dose of 1.7 mg terlipressin every 24 hours and increased to a maximum of 10.2 mg terlipressin every 24 hours. If volume expansion is needed, GLYPRESSIN can be diluted before administration (see section – Preparation of diluted solution). Administration of terlipressin as continuous IV infusion has been associated with lower rates of adverse events than with administration by IV bolus (see section 5.1 – PHARMACODYNAMIC PROPERTIES – Clinical Trials).

Preparation of diluted solution (For HRS indication only)
The terlipressin daily dose can be diluted using aseptic technique in up to 250 mL of sodium chloride 9mg/mL (0.9%) or glucose 50 mg/mL (5%) before administration.

The diluted solution is stable for up to 24 hours at 25°C, however it is not intended to be stored.
To reduce microbiological hazard, use as soon as practicable after dilution. The 24-hour period only reflects the in-use stability during infusion and does not imply that the diluted product may be stored prior to administration.

The diluted product is incompatible with polyurethane (PUR) infusion lines. It is recommended to use polyvinyl chloride (PVC) or polyethylene (PE) infusion lines.

4.3 CONTRAINDICATIONS

Pregnancy.

Hypersensitivity to terlipressin or any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Patient with cardiovascular and pulmonary disease

Particular care is required in management of patients with cardiovascular or pulmonary disease since terlipressin may induce ischaemia and pulmonary vascular congestion.

Caution should also be exercised in treating patients with hypertension.

Monitoring during treatment

During treatment, regular monitoring of blood pressure, ECG or heart rate, oxygen saturation, serum levels of sodium and potassium, as well as fluid balance are required.

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.

Excipients

This medicinal product contains 1.33 mmol (or 30.7 mg) of sodium per ampoule which should be taken into consideration in patients on a controlled sodium diet.

Sepsis/septic shock

Cases of sepsis/septic shock, including fatal cases, have been reported in patients treated with terlipressin for type 1 HRS. Causal association to terlipressin has not been established. Patients should be monitored daily for any signs or symptoms suggestive of infection.

Terlipressin should not be used in patients with septic shock with a low cardiac output.

Injection site reaction

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

Skin necrosis

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

Torsades de Pointes

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including "Torsades de Pointes" have been reported (see Section 4.8 – ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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, or concomitant medications that can prolong the QT interval (see Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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). Fatal cases of respiratory failure, including respiratory failure due to fluid overload, have been reported in patients treated with terlipressin for Type 1 HRS. 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 HRS. 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.

Use in renal impairment

Prior to treatment of Type 1 HRS, other types of acute kidney injury should be ruled out.

Terlipressin should be used with caution in patients with renal impairment. Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442 micromoles/L (5.0 mg/dL), when treated with terlipressin for Type 1 HRS, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of HRS, increased risk of adverse events, and increased mortality in this patient group have been observed in clinical trials.

Use in 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 HRS, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of HRS, increased risk of respiratory failure, and increased mortality in this patient group have been observed in clinical trials.

Use in the elderly

Because of limited experience, special precaution should be taken during treatment of elderly patients. No data is available regarding dosage recommendation in this special patient category.

Paediatric use

Because of limited experience, special precaution should be taken during treatment of children. No data is available regarding dosage recommendation in this special patient category.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Terlipressin increases the hypotensive effect of non-selective beta 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 "Torsades de Pointes" (see Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 - ADVERSE EFFECTS (UNDESIRABLE 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).

4.6 FERTILITY, PREGNANCY AND LACTATION

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 IV; 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 IV. 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 pregnancy and the fetus.

Spontaneous abortion and fetal malformations were observed in pregnant rabbits treated with terlipressin throughout organogenesis at IV 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.

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 ADVERSE EFFECTS (UNDESIRABLE 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.

Table 1: The adverse effects reported in the post-marketing period.

There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications.

MedDRA System Organ Class Disorder	**Very common (>10 %)**	**Common (≥1 % & <10 %)**	**Uncommon (≥0.1 % & <1 %)**	**Rare (≥0.01 % & <0.1 %)**	**Frequency not known[a]**
INFECTIONS AND INFESTATIONS		Sepsis/septic shock[b, c]			
METABOLISM		Hyponatraemia			
NERVOUS SYSTEM		Headache			
CARDIAC		Chest pain; Bradycardia; Tachycardia	Atrial fibrillation; Ventricular extrasystoles[d]; Myocardial infarction; Torsades de Pointes; Cardiac failure;	Ventricular fibrillation	
VASCULAR		Vasoconstriction; Peripheral ischemia; Pallor; Hypertension; Cyanosis	Hot flushes		
RESPIRATORY	Respiratory failure[b]; Dyspnoea[b]	Pulmonary oedema; Respiratory distress[b]; Dyspnoea[e]	Respiratory distress[e]; Respiratory failure[e]		

MedDRA System Organ Class Disorder	Very common (>10 %)	Common (≥1 % & <10 %)	Uncommon (≥0.1 % & <1 %)	Rare (≥0.01 % & <0.1 %)	Frequency not known[a]
GASTROINTESTINAL	Abdominal pain	Diarrhoea; Nausea; Vomiting	Intestinal ischaemia		
SKIN AND SUBCUTANEOUS			Skin necrosis (unrelated to the site of administration)[c, d]		
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS					Uterine hypertonus; Uterine ischaemia
GENERAL			Injection site necrosis		

[a] Frequencies of these adverse events cannot be estimated from the available data.
[b] Applicable to Type 1 HRS. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials.
[c] See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further information.
[d] Adverse reactions identified from post-marketing sources are presented by frequency category based on a theoretically calculated frequency if not observed in clinical trials.
[e] Applicable to bleeding oesophageal varices.

Safety related to method of administration

Based on results from a dedicated randomised controlled multicentre trial on use in Type 1 HRS, administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see sections 4.2 Dose and Method of Administration and 5.1 Pharmacodynamic Properties – Clinical Trials).

Reporting suspected adverse events

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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The recommended dose of 1.7 mg 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 micrograms clonidine IV.

Bradycardia requiring treatment should be treated with atropine.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 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 is more effective than 0.85 mg, 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 V1a receptors on vascular smooth muscle in the splanchnic and portal circulation. Moreover, terlipressin can also act via V1a 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 V2 receptors. V2 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 V1b receptors has been observed as illustrated by no significant effects observed on adrenocorticotropic hormone and cortisol release.

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 IV 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 IV 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 IV 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 (ICU). 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 0.79 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 class 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 IV 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 IV injection followed by 1 mg injections every 6 h for a total of 72 h of treatment) or with octreotide (initial 100 mg IV injection and 50 mg/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 4.2 DOSE AND METHOD OF 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:

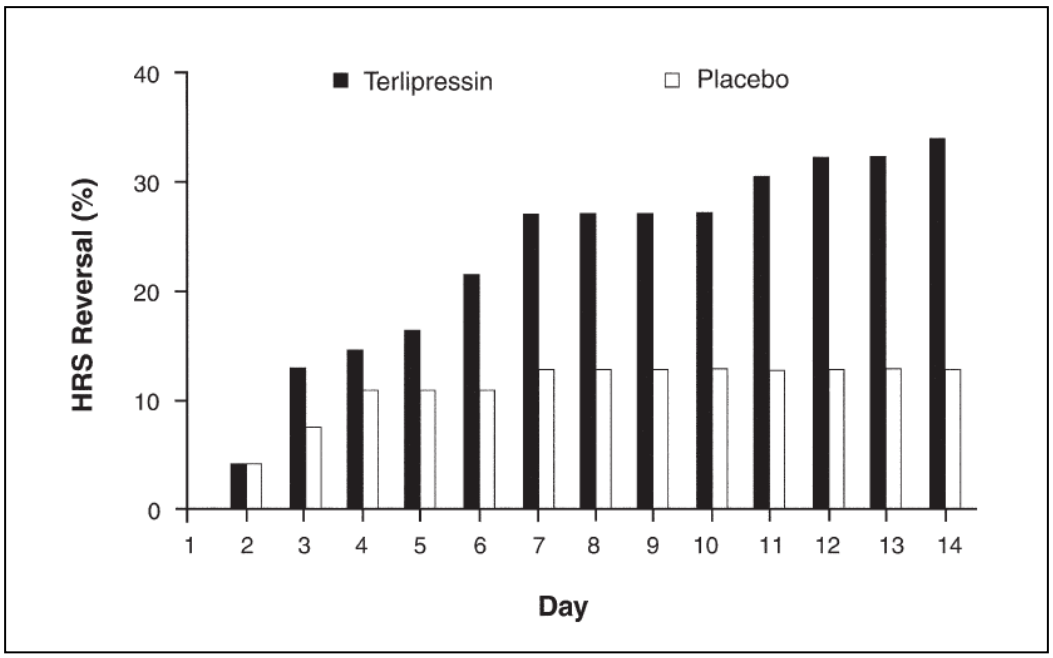
The study of Sanyal *et al.* (2008) was a prospective, randomised, double-blind, placebo-controlled multicentre, phase III study in 112 HRS type 1 patients who were randomised in a 1:1 ratio to receive either intravenous terlipressin via slow intravenous push at an initial dose of 0.85 mg every 6 hours or matching placebo for a period of up to 14 days. Dose was increased to 1.7 mg every 6 hours 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 micromoles/L], total bilirubin 15.4 mg/dL [263.3 micromoles/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 micromoles/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 micromoles/L] during treatment without dialysis); and survival up to 180 days. Treatment outcomes are shown in the Table 2, cumulative incidence of HRS reversal in Figure 1.

Table 2: 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).

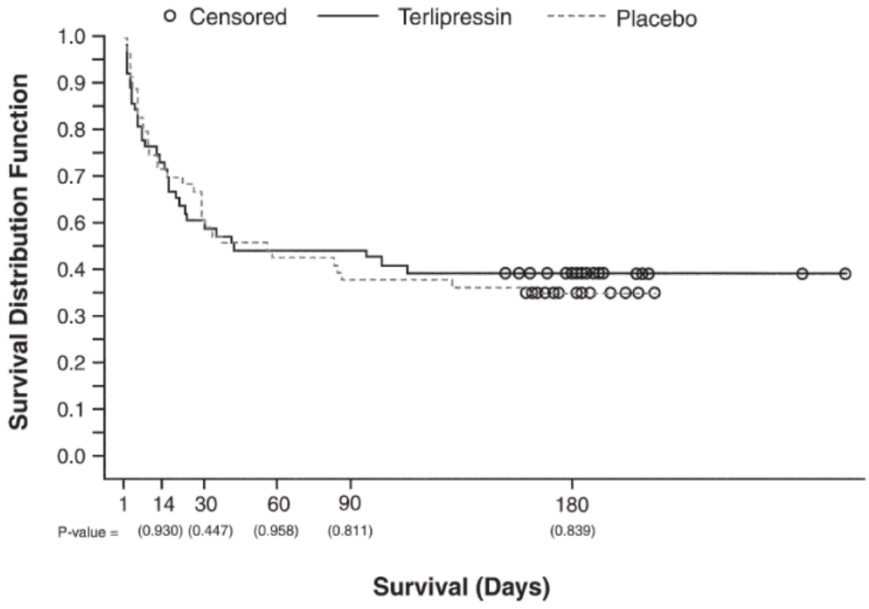
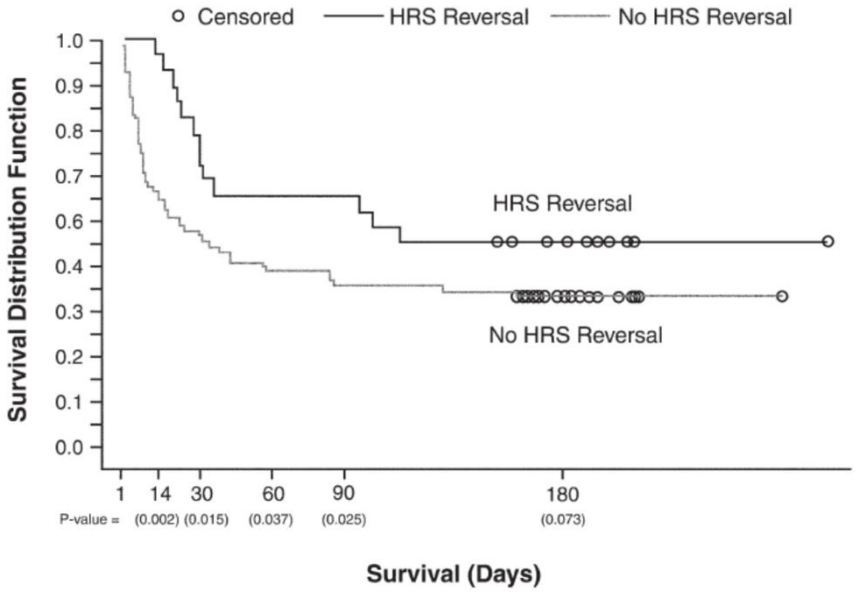


Figure 3. Overall survival for HRS reversal vs no HRS reversal
Observations were censored at the last time a patient was known to be alive (represented by *open circles*). All patients are included irrespective of treatment.



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 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.

<u>Continuous intravenous infusion versus intravenous boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis</u>

The safety of continuous intravenous infusion of terlipressin has been compared with intravenous bolus in an open-label randomised controlled multicentre trial. Seventy-eight patients with type 1 hepatorenal syndrome were randomly assigned to either continuous intravenous infusion at the initial dose of 2 mg/day or intravenous boluses of terlipressin at the initial dose of 0.5 mg every 4 hours. In case of no response, the dose was progressively increased to a final dose of 12 mg/day in both groups. Albumin was given at the same dose in both groups. The primary endpoint was defined as the prevalence of treatment-related adverse events (AEs) between the two groups. Both the total rate of treatment-related AEs as well as severe treatment-related AEs were lower in the continuous infusion group than in the bolus group (all treatment-related AEs: 12/34 patients (35%) vs 23/37 patients (62%), $p<0.025$. Severe treatment-related AEs: 7/34 patients (21%) vs 16/37 patients (43%); $p<0.05$). The rate of response to terlipressin was not statistically significantly different between the continuous infusion and bolus groups (76% vs 65%). The probability of 90-day transplant-free survival was not significantly different between the continuous infusion group and the bolus group (53% vs 69%).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of terlipressin have been investigated in healthy volunteers and in cirrhotic patients, with similar PK characteristics observed in both populations.

Distribution

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.

Metabolism and excretion

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.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride, acetic acid, sodium acetate trihydrate, water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except for those stated in section 4.2 – Dose and Method of Administration -Preparation of diluted solution (For HRS indication only).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 2°C - 8°C in the original packaging to protect from light.

Reconstituted solution: The product should be used immediately after reconstitution.

The diluted solution is stable for up to 24 hours at 25°C, however it is not intended to be stored.

To reduce microbiological hazard, it should be used immediately after reconstitution. The 24-hour period only reflects the in-use stability during infusion and does not imply that the diluted product may be stored prior to administration.

6.5 NATURE AND CONTENTS OF CONTAINER

GLYPRESSIN Solution for Injection, ampoule:

8.5 mL clear, colourless solution in a clear glass ampoule, containing 0.85 mg terlipressin. Supplied in a box containing 5 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

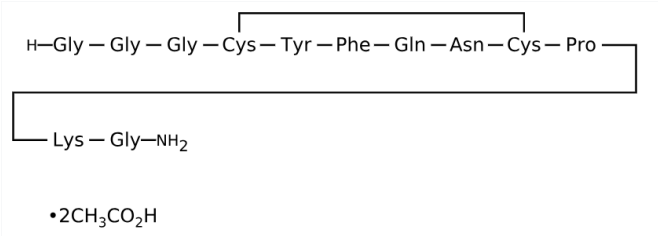
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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 pKa is approximately 10.

Chemical structure



The chemical name is *N*-[*N*-(*N*-Glycylglycyl) glycyl]-8-L-lysinevasopressin. It is available as an acetate.

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

CAS number

914453-96-6.

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8 SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll Free: 1800 337 746

9 DATE OF FIRST APPROVAL

14 May 2012

10 DATE OF REVISION

07 May 2026

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

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Summary table of changes

Section Changed	Summary of new information
2	Removed reference to concentration of the drug product in mg/mL.
4.2	Type 1 HRS: Addition of IV infusion as an alternative method of administration, including instructions for preparation of diluted solution. Incompatibility of diluted product with polyurethane (PUR) infusion lines added. Removal of albumin quantity for administration and added reference to current guidelines. Removal of standard duration of treatment.
4.3	Removal of contraindication in patients with current or recent ischaemic cardiovascular disease.
4.8	Addition of statement on “Safety related to method of administration”.
5.1	Addition of clinical trial: “Continuous intravenous infusion versus intravenous boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis”.
6.2	Incompatibility statement regarding diluted terlipressin solution.
6.4	Storage and usage instruction for diluted solution.
6.7	Chemical structure, chemical name and CAS number updated.
All	Minor Editorial Changes