**AUSTRALIAN PRODUCT INFORMATION**
**LUCASSIN terlipressin 0.85 mg powder for injection vial**

## 1. NAME OF THE MEDICINE:

Terlipressin

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of LUCASSIN contains 0.85 mg terlipressin free base and approximately two equivalents (0.084 mg) of acetic acid. Thus, the drug substance is present mainly in the form of terlipressin diacetate. Terlipressin diacetate is freely soluble in water; pKa 10.01 calculated.

Mannitol is used as the caking agent; glacial acetic acid and/or sodium hydroxide are used to adjust the pH to achieve a final product pH of 4.3 - 7.5.

For the full list of excipients, see Section 6.1 List of Excipients

## 3. PHARMACEUTICAL FORM

LUCASSIN is supplied as a sterile, lyophilized powder for injection in single-use clear glass vials for intravenous administration. Each vial must be reconstituted with 5mL of 0.9% sodium chloride injection prior to use.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

LUCASSIN is indicated for the treatment of patients with

- hepatorenal syndrome (HRS) type 1 who are actively being considered for a liver transplant
- bleeding oesophageal varices

### 4.2 DOSE AND METHOD OF ADMINISTRATION

LUCASSIN must be administered intravenously.

***Hepatorenal Syndrome Type 1 (HRS-1)***

The recommended starting dose is 0.85 mg terlipressin every 6 hours by slow intravenous bolus injection. If serum creatinine (SCr) has not decreased by at least 30% from the baseline value after 3 days, the dose can be increased to 1.7 mg terlipressin every 6 hours.

It is recommended that the dose should 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 with LUCASSIN should be continued until about 2 days after the patient achieves

HRS reversal (SCr ≤132.6 µmol/L). Treatment should be terminated if the patient undergoes dialysis or liver transplant or if serum creatinine remains at or above baseline after 7 days of treatment. The initial treatment course may be continued for up to two weeks.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction. When the patient's symptoms resolve, LUCASSIN 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 - 2.55 mg terlipressin/day. The maximum dose studied (TAHRS Study) was 1.7 mg terlipressin every 4 hours.

***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 terlipressin 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.

Each vial of LUCASSIN is intended for single use in one patient only.

**Instructions for IV Administration**

Reconstitute each vial with 5 mL of sterile 0.9% sodium chloride injection prior to administration to prepare a 0.85 mg/5mL terlipressin solution. Do not use dextrose solutions to reconstitute the vial. Administer LUCASSIN as a slow IV bolus. Flush the line with saline prior to and after the LUCASSIN bolus injection.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. If not administered immediately, the reconstituted solution should be refrigerated (2 - 8°C) up to 24 hours prior to use.

## 4.3 CONTRAINDICATIONS

Hypersensitivity to terlipressin or any of the excipients.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Cardiovascular Effects**
Use with caution in patients with coronary artery disease as terlipressin may cause myocardial ischaemia. 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 rarely. 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

**Ischaemic Events**
Ischaemic events (cardiac, gastrointestinal, and skin) have occurred following administration of terlipressin and may require temporary interruption, dose decrease or permanent discontinuation of terlipressin. Manifestations may include angina, ECG changes, severe abdominal pain with gastrointestinal bleeding, peripheral cyanosis and extremity pain.

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**
Due to its constrictive effects on smooth muscle, terlipressin should be used with caution in patients with severe asthma or chronic obstructive pulmonary disease (COPD). Patients with these disorders who require terlipressin should be closely monitored and any bronchospasm should be treated symptomatically.

**Laboratory Monitoring**
Serum creatinine levels should be monitored daily to assess response to therapy. Serum electrolytes should be monitored periodically as hyponatraemia, hypokalaemia, hypomagnesaemia and other electrolyte disturbances have been reported.

**Use in renal impairment**
Patients with HRS type 1 have significant renal impairment. In study OT-0401 6 of the 56 terlipressin-treated patients (11%) with a serum creatinine greater than 618.8 µmol/L, failed to achieve HRS reversal.

**Use in the elderly**
Of the total number of patients randomised to receive terlipressin in clinical studies in HRS-1, 15% were ≥65 years of age and 3% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and the younger patients, but the number of patients treated is too small to draw definitive conclusions and greater sensitivity of some older individuals cannot be ruled out.

**Paediatric Use**
Safety and effectiveness in paediatric patients have not been established.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been conducted.

Terlipressin is not metabolised by cytochrome P450 isoenzymes, nor does it induce or inhibit this enzyme system in human liver microsomes *in-vitro*. Isoenzymes tested for inhibitory and induction potential include: CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4; in addition, for inhibitory potential only: CYP2C8.

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 "Torsade de pointes" (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 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).

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on Fertility**
No specific studies with terlipressin have been conducted in animals to evaluate the effect on fertility. Reduced testicular weights and seminiferous tubular degeneration were seen in rats that received intravenous injections of 0.5 mg/kg/day or greater of terlipressin. Exposure (based on AUC) at the no-effect level was less than that anticipated at the clinical dose of 0.85 mg every 6 hours.

**Use in Pregnancy** (Category D)

Terlipressin may cause foetal harm when administered to pregnant women. In three published clinical trials (two in pregnant women and one in non-pregnant women), terlipressin caused significant increases in uterine activity and reduction in endometrial blood flow. These adverse effects pose significant foetal risk through spontaneous abortion, resorption and the potential for development of various birth defects.

In published animal studies, terlipressin and other vasopressin analogues reduced blood flow to the uterus and placenta resulting in foetal death and/or abortion, and foetal abnormalities due to local tissue hypoxia. Administration of terlipressin (3-10 mcg/kg) to pregnant guinea pigs caused a marked decrease in blood flow to the uterus and placenta. As these effects are mediated by pharmacological action, terlipressin may have harmful effects on pregnancy and on the developing foetus.

**Use in Lactation**
It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued in women receiving terlipressin therapy.

## 4.7 EFFECTS ON ABILITY TO DRIVE OR USE MACHINES

The effects of this medicine on a person's ability to drive and use machines was not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse reactions are discussed in greater detail in the Section 4.4 Special Warnings and Precautions for Use: cardiovascular effects, ischaemic events and respiratory effects.

### Hepatorenal Syndrome

### Adverse Events

Table 1 summarises all adverse events that occurred in at least three terlipressin-treated patients and more frequent than placebo or albumin in either of the two controlled clinical trials in patients with HRS.

**Table 1. Adverse Events in At Least 3 Patients and Occurring More Frequently in the Terlipressin Group in either OT-0401 or TAHRS Safety Population**

| | OT-0401 | | TAHRS | |
|---|---|---|---|---|
| | Terlipressin (N=56) n (%) | Placebo (N=55) n (%) | Terlipressin + Albumin (N=23) n (%) | Albumin (N=23) n (%) |
| Vomiting | 9 (16.1) | 2 (3.6) | 1 (4.3) | 3 (13.0) |
| Abdominal pain | 7 (12.5) | 4 (7.3) | 5 (21.7) | 1 (4.3) |
| Diarrhoea | 3 (5.4) | 2 (3.6) | 7 (30.4) | 2 (8.7) |
| Flatulence | 3 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Intestinal ischaemia | 0 (0.0) | 0 (0.0) | 3 (13.0) | 0 (0.0) |
| Wheezing/bronchospasm | 6 (10.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Dyspnoea/dyspnoea exacerbated | 5 (8.9) | 2 (3.6) | 3 (13.0) | 0 (0.0) |
| Pneumonia/fungal pneumonia | 4 (7.1) | 0 (0.0) | 0 (0.0) | 1 (4.3) |
| Acute pulmonary oedema/pulmonary oedema | 4 (7.1) | 3 (5.5) | 4 (17.4) | 1 (4.3) |
| Respiratory failure | 3 (5.4) | 2 (3.6) | 0 (0.0) | 0 (0.0) |
| Epistaxis | 3 (5.4) | 1 (1.8) | 0 (0.0) | 0 (0.0) |
| Sepsis/septic shock/sepsis syndrome/enterococcal sepsis/clostridium difficile sepsis | 7 (12.5) | 1 (1.8) | 2 (8.7) | 1 (4.3) |
| Hypomagnesaemia | 4 (7.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hepatic failure | 8 (14.3) | 7 (12.7) | 3 (13.0) | 3 (13.0) |
| Headache | 4 (7.1) | 2 (3.6) | 0 (0.0) | 0 (0.0) |
| Supraventricular tachycardia | 3 (5.4) | 2 (3.6) | 0 (0.0) | 0 (0.0) |
| Bradycardia | 3 (5.4) | 0 (0.0) | 1 (4.3) | 1 (4.3) |

| | | | | |
|---|---|---|---|---|
| Pyrexia | 3 (5.4) | 1 (1.8) | 1 (4.3) | 1 (4.3) |
| Multi-organ failure | 4 (7.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Anxiety | 4 (7.1) | 1 (1.8) | 0 (0.0) | 0 (0.0) |
| Hypotension | 4 (7.1) | 3 (5.5) | 0 (0.0) | 0 (0.0) |
| Pain in extremity | 3 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fluid overload | 2 (3.6) | 1 (1.8) | 3 (13.0) | 2 (8.7) |

Less common serious and/or clinically relevant adverse events that occurred in less than 3 terlipressin-treated patients in these trials include:

Myocardial infarction, myocardial ischaemia, ventricular tachycardia, hypertension, peripheral cyanosis and livedo reticularis.

Adverse events from 35 published literature studies, case reports and abstracts in HRS patients are provided in Table 2.

**Table 2. Adverse Events Reported in the Literature in Case Reports and Studies Where Occurrence was Given* (HRS Patients)**

| ADVERSE EVENT (MEDDRA PT) | N | %* | ADVERSE EVENT (MEDDRA PT) | N | %* |
|---|---|---|---|---|---|
| Abdominal pain | 56 | 10.73% | Hypertension | 2 | 0.38% |
| Frequent bowel movements | 30 | 5.75% | Intestinal ischaemia | 2 | 0.38% |
| Diarrhoea | 24 | 4.60% | Lymphangitis | 2 | 0.38% |
| Arrhythmia | 9 | 1.72% | Myocardial ischaemia | 2 | 0.38% |
| Peripheral ischaemia | 8 | 1.53% | Pulmonary oedema | 2 | 0.38% |
| Skin necrosis | 8 | 1.53% | Tongue disorder (Tongue ischaemia) | 2 | 0.38% |
| Chest pain | 7 | 1.34% | Acute myocardial infarction | 1 | 0.19% |
| Tachycardia | 6 | 1.15% | Electrocardiogram ST segment depression | 1 | 0.19% |
| Cyanosis | 5 | 0.96% | Gangrene | 1 | 0.19% |
| Fluid overload | 5 | 0.96% | Hepatic enzyme increased | 1 | 0.19% |
| Bronchospasm | 4 | 0.77% | Pancreatitis | 1 | 0.19% |
| Injection site necrosis | 4 | 0.77% | Rectorrhagia | 1 | 0.19% |
| Bradycardia | 2 | 0.38% | Sudden death | 1 | 0.19% |
| Dyspnoea | 2 | 0.38% | Vomiting | 1 | 0.19% |

*Among 522 patients. Studies where incidence of AEs are not reported have been excluded from this total.

## Adverse Reactions

**Table 3. Adverse Reactions (Treatment-Related) Reported in At Least 2 Patients Receiving Terlipressin and More Frequent than Placebo/Control in either OT-0401 or TAHRS Safety Population**

| | OT-0401 | | TAHRS | |
|---|---|---|---|---|
| | Terlipressin (N=56) n (%) | Placebo (N=55) n (%) | Terlipressin + Albumin (N=23) n (%) | Albumin (N=23) n (%) |
| Gastrointestinal | | | | |
| Nausea | 3 (5.4) | 3 (5.5) | 2 (8.7) | 0 (0.0) |
| Abdominal pain | 2 (3.6) | 2 (3.6) | 5 (21.7) | 0 (0.0) |
| Diarrhoea | 0 (0.0) | 0 (0.0) | 7 (30.4) | 2 (8.7) |
| Intestinal ischaemia | 0 (0.0) | 0 (0.0) | 3 (13.0) | 0 (0.0) |
| Rectal haemorrhage | 0 (0.0) | 0 (0.0) | 2 (8.7) | 0 (0.0) |
| Respiratory | | | | |
| Dyspnoea | 0 (0.0) | 0 (0.0) | 3 (13.0) | 0 (0.0) |
| Pulmonary oedema[a] | 4 (7.1) | 3 (5.5) | 4 (17.4) | 1 (4.3) |
| Respiratory distress | 2 (3.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Metabolism and Nutrition | | | | |
| Fluid overload | 0 (0.0) | 0 (0.0) | 3 (13.0) | 2 (8.7) |
| Anorexia | 0 (0.0) | 0 (0.0) | 2 (8.7) | 0 (0.0) |
| Hypertension | 0 (0.0) | 0 (0.0) | 2 (8.7) | 0 (0.0) |

[a]: pulmonary oedema includes acute pulmonary oedema

There were no treatment-related deaths in either OT-0401 or TAHRS studies.

There were 2 treatment-related deaths reported in the literature for HRS: one each due to bronchospasm and sudden death, both were described in retrospective analyses.

## Bleeding Oesophageal Varices

Safety data related to this indication are available from the published literature and post-marketing experience as described below. Post-marketing adverse event data have generally been collected for other formulations of terlipressin for this indication,

## Clinical Trials

Three studies assessed safety as the primary outcome in a total of 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). Table 4 below lists the adverse effects reported for terlipressin in the post-marketing period.

**Table 4. Adverse Reactions from Post-Marketing Surveillance**

| MedDRA System Organ Class Disorder | Common (≥1% & <10%) | Uncommon (≥0.1% & <1%) | Rare (≥0.01% & <0.1%) |
|---|---|---|---|
| METABOLISM | | Hyponatraemia if fluid not monitored | |
| NERVOUS SYSTEM | Headache | | |
| CARDIAC | Bradycardia | Atrial Fibrillation; Ventricular Extrasystoles; Tachycardia; Cardiac failure; Chest pain; Myocardial Infarction; Torsade de pointes; Fluid overload with pulmonary oedema. | Ventricular fibrillation |
| 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; uterine ischemia | |

| | | | |
|---|---|---|---|
| GENERAL | | Injection site necrosis | |

Adverse reactions which caused or contributed to fatal outcome: intestinal ischaemia, injection site necrosis, skin necrosis, gastrointestinal haemorrhage, respiratory insufficiency, pulmonary oedema, circulatory failure, myocardial ischaemia, sudden death, cyanosis, acidosis, lactic acidosis, ventricular fibrillation and cardiac arrest.

Other clinically significant adverse reactions: prolonged QT interval, Torsade de pointes, hypertension, bradycardia, hyponatraemia, hypokalaemia, livedo reticularis, peripheral ischaemia, vasospasm, rhabdomyolysis, achrocyanosis, Tako-Tsubo cardiomyopathy and arrhythmia.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 http://www.tga.gov.au/reporting-problems.

**Immunogenicity**
Blood samples were drawn from the patients in study OT-0401 at baseline & at days 14, 30 and 60. The plasma was analysed for anti-terlipressin antibody titer using an enzyme-linked immunosorbent assay (ELISA). No significant levels of antibody to terlipressin were detectable in any of the patient specimens tested.

## 4.9 OVERDOSE

There are no published reports of overdose with terlipressin. Manifestations of terlipressin overdose are expected to be similar to the adverse effects profile described for therapeutic doses. Treatment should be symptomatic, with close monitoring of electrolytes, fluid balance and cardiovascular system.

The recommended dose of 1.7 mg terlipressin 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 IV.

Bradycardia requiring treatment can be treated with atropine.

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

## Mechanism of Action

Hepatorenal syndrome (HRS) is caused by intra-renal vasoconstriction and circulatory dysfunction characterised by vasodilation in the splanchnic circulation leading to hypoperfusion of the kidneys. As a result, renal perfusion and glomerular filtration rate are greatly reduced, but tubular function is preserved.

Terlipressin is a synthetic vasopressin analogue that acts as a systemic vasoconstrictor, via vasopressin 1a ($V_{1a}$) receptors, both as a prodrug for lysine-vasopressin and having pharmacologic activity on its own, albeit of lower potency than lysine-vasopressin. In HRS patients with hyperdynamic circulation, the $V_1$ receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic area, results in an increase in mean arterial pressure (MAP), normalisation of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system), and an increase in renal blood flow. The therapeutic rationale for treatment of HRS with terlipressin is that these effects may result in improved renal function.

## Pharmacodynamics

Terlipressin increases MAP and decreases heart rate while increasing systemic vascular resistance. The terlipressin-treated patients in clinical study OT-0401 described in the **Clinical Trials** section below experienced a significant difference in MAP between responders and non-responders from baseline through end of treatment (OT-0401: +8.3 mmHg, p=0.025). In clinical study OT-0401, there were small transient increases in MAP following each dose of terlipressin. These transient increases were not associated with HRS reversal, suggesting that it is not feasible to guide dosing by measuring post-dose blood pressure.

*Cardiac Electrophysiology:* Changes in QT intervals were assessed in 41 terlipressin-treated patients with HRS type 1 enrolled in the OT-0401 study. The time-averaged placebo-corrected change from baseline on QTcF was +8 msec.

## Clinical Trials

### Hepatorenal Syndrome Type 1

The efficacy and safety of terlipressin to improve renal function in patients with hepatorenal syndrome type 1 was assessed in one pivotal multicenter, randomised, controlled study (OT-0401), and was supported by an open-label, multicenter, randomised study (TAHRS).

### Study OT-0401:

This pivotal multicenter, double-blind, placebo-controlled study randomised 112 HRS type 1 patients in a 1:1 ratio to receive either intravenous terlipressin at an initial dose of 0.85 mg (one vial of LUCASSIN) every 6 hours or matching placebo for a period of up to 14 days. Baseline data were similar between the 2 groups. Ninety-one percent of patients in each group also received intravenous albumin for plasma volume expansion. The mean patient age was 52 years (range 23 to 74), 71% were male, 89% were Caucasian, and 12% were of Hispanic/Latino ethnicity. The primary causes of cirrhosis were alcohol (52%) and hepatitis C (37%). Other relevant baseline parameters were (mean): Child-Pugh score 11.4, MELD score 33.4, serum creatinine 344.8 µmol/L, total bilirubin 263.3 µmol/L.

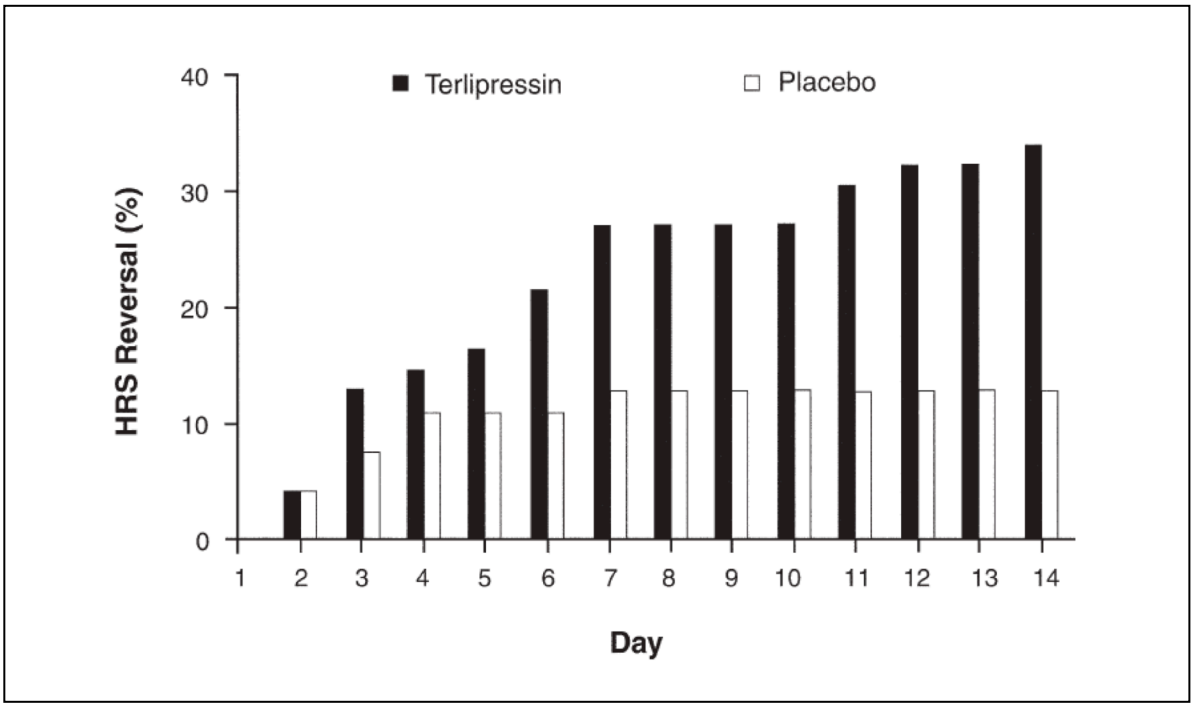
Patients were monitored for up to 180 days after administration of first dose. Primary endpoints included: Treatment success at Day 14 (two serum creatinine [SCr] levels ≤132.6 µmol/L 48 ± 24 h apart without intervening SCr ≥221 µmol/L, liver transplant or dialysis up to Day 14); HRS reversal on treatment (SCr level ≤132.6 µmol/L). Other endpoints included change in SCr from baseline to day 14; and survival up to 180 days. Treatment outcomes for the renal function endpoints are shown in Table 5. The cumulative incidence of HRS reversal is presented in Figure 1.

**Table 5. OT-0401 − Treatment Outcomes for Renal Function Endpoints**

| Outcome | Terlipressin (n=56) | Placebo (n=56) | p-value |
|---|---|---|---|
| Treatment success at Day 14, n (%)[a] (95% C.I.) | 16 (28.6) (17.3, 42.2) | 7 (12.5) (5.2, 24.1) | 0.037[b] |
| HRS reversal, n (%) (95% C.I.) | 19 (33.9) (21.8, 47.8) | 7 (12.5) (5.2, 24.1) | 0.008[b] |
| Change in SCr, µmol/L[c] (95% C.I.) | 62.4 (16.4) (-94.96, -29.88) | 1.1 (16.4) (-31.46, 33.58) | 0.006[d] |

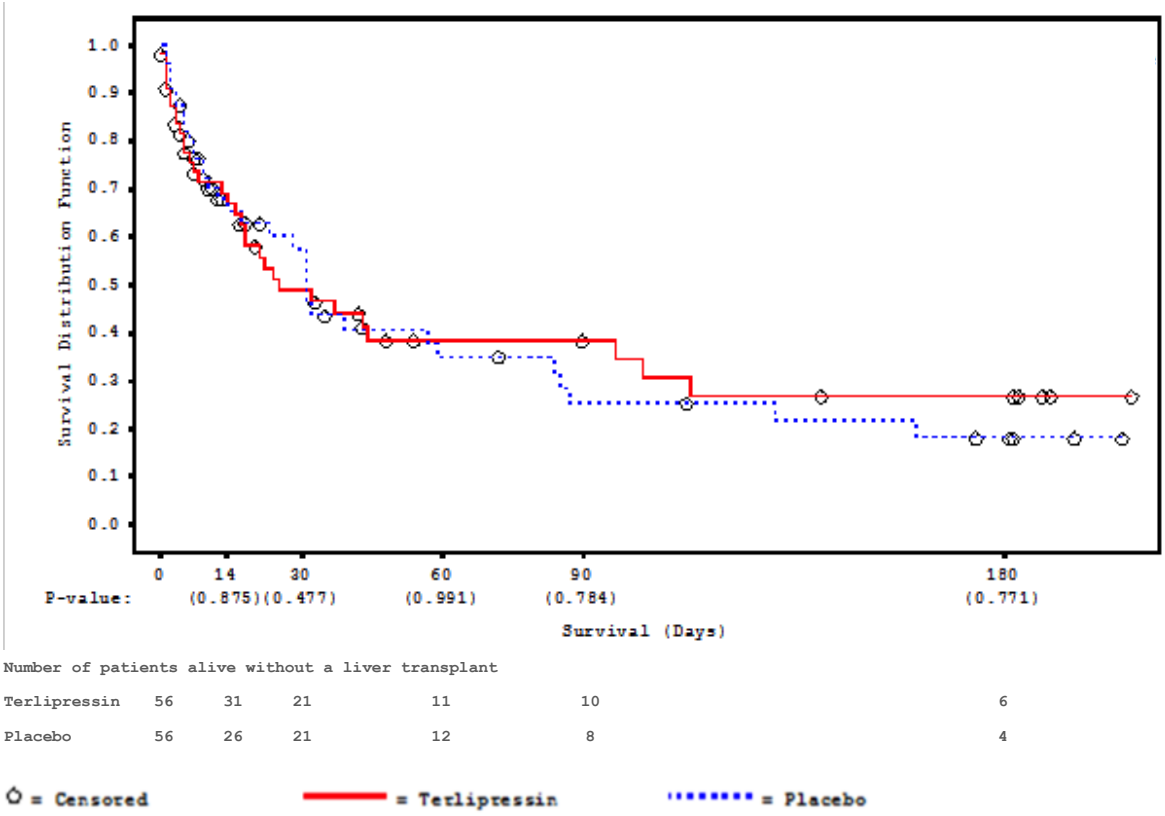
[a]Incorporates additional SCr data collected after initial database closure
[b]From a stratified Cochran-Mantel-Haenszel (CMH) test.
[c]Least Square Mean (SE) for change from baseline to Day 14.
[d]p-value comparing treatment groups, from repeated measures ANOVA.

**Figure 1. OT-0401 − Cumulative Incidence of HRS Reversal by Day. (Treatment began on day 1)**



***Survival***: Study OT-0401 included survival as non-primary endpoints for which adequate powering was not possible due to the rarity of HRS type 1. Overall survival at day 180 was 43% for terlipressin and 38% for placebo (p=NS). Transplant-free survival at day 180 was 27% for terlipressin and 18% for placebo (p=NS) (Figure 2). Analysis of overall survival and transplant-free survival rates for HRS reversal responders vs. non-responders for each treatment group showed a separation in both survival distributions among responders and non-responders. Patients on terlipressin achieving HRS reversal exhibited significantly longer rates of overall survival to day 90 (p=0.027) and significantly longer transplant-free survival (p=0.008) through day 180.

**Figure 2. OT-0401 - Transplant-free survival up to Day 180 (ITT population)**




**TAHRS Study:**

This supportive open-label, multicenter study randomised 46 of the planned 100 patients in a 1:1 ratio to receive either intravenous terlipressin at an initial dose of 0.425 - 0.85 mg (equivalent of half to one vial of LUCASSIN) every 4 hours plus 20% albumin, or only 20% albumin for a maximum of 15 days. The study was terminated early following a protocol-specified interim futility analysis of survival and insufficient enrollment. The majority of patients had HRS type 1 (74%) and the remainder, severe HRS-2 (i.e. hospitalised patients with a baseline SCr ≥176.8 µmol/L). Analyses of HRS reversal on treatment (SCr levels ≤132.6 µmol/L), change in SCr from baseline to end of randomised treatment, and responder survival produced consistent findings with those of the pivotal study OT-0401.

**Bleeding Oesophageal Varices**

The data evaluated for this indication were from a literature-based submission which retrieved publications related to efficacy and dose ranging. The key studies for 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); a supportive, controlled study involving oesophageal variceal band ligation (Abid et al, 2009) and a supportive 3-way randomised comparison of terlipressin, octreotide and somatostatin (Seo et al, 2014). 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. Reference to doses of 1mg and 2mg in the following section relate to 1 mg or 2 mg of terlipressin acetate (0.85 or 1.7 mg of terlipressin, respectively).

***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. 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 C, the patient survived.

***Supportive studies versus active comparators, in addition to endoscopic treatment***

Seo et al, 2014 conducted a multicentre, randomised, non-inferiority trial to characterise the effects of terlipressin, somatostatin, and octreotide when they are initiated before endoscopic

treatment in patients with acute variceal bleeding. Patients with liver cirrhosis and significant upper gastrointestinal bleeding were randomly assigned to receive early administration of terlipressin, somatostatin, or octreotide, followed by endoscopic treatment. Patients with nonvariceal bleeding were excluded after endoscopy. The primary endpoint was 5-day treatment success, defined as control of bleeding without rescue treatment, rebleeding, or mortality, with a noninferiority margin of 0.1.

In total, 780 patients with variceal bleeding were enrolled: 261 in the terlipressin group; 259 in the somatostatin group; and 260 in the octreotide group. At the time of initial endoscopy, active bleeding was noted in 43.7%, 44.4%, and 43.5% of these patients, respectively (p = 0.748), and treatment success was achieved by day 5 in 86.2%, 83.4%, and 83.8% (p = 0.636), with similar rates of control of bleeding without rescue treatment (89.7%, 87.6%, and 88.1%; p = 0.752), rebleeding (3.4%, 4.8%, and 4.4%; p = 0.739), or mortality (8.0%, 8.9%, and 8.8%; p = 0.929). The absolute values of the lower bound of confidence intervals for terlipressin versus somatostatin, terlilpressin versus octreotide, and octreotide versus somatostatin were 0.095, 0.090, and 0.065, respectively.

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 µg IV 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 Section 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.

## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of terlipressin was evaluated in 29 patients with HRS type 1 in the OT-0401 study using population pharmacokinetic analyses.

**Absorption**
The mean maximum terlipressin concentration of 62.1 ng/mL was observed immediately after dosing (0.85 mg), then decayed rapidly with a mean half-life of 1 hour and returned to baseline within the 6-hour dosing interval.

**Distribution**
The mean maximum lysine-vasopressin steady-state plasma level was 1 ng/mL, and was reached at approximately 2 hours post dose. In HRS patients, terlipressin and lysine-vasopressin plasma concentrations appear to increase with dose from 0.85 mg to 1.7 mg (terlipressin free base) every 6 hours. Despite having significantly compromised hepatic and renal function, HRS patients seem to have a metabolic and pharmacokinetic disposition of terlipressin that is similar to healthy volunteers.

Due to the short half-life and rapid clearance of terlipressin (0.375 L/h/kg) in HRS patients, the chance of significant drug accumulation is very low.

**Metabolism**
Cleavage of the N-terminal glycyl residues of terlipressin by various tissue peptidases results in release of lysine-vasopressin. Terlipressin is almost completely metabolised in tissue (not plasma). Lysine-vasopressin is metabolised at the C- and N-terminus by various peptidases and proteases that are detectable in almost all human tissues; however, the majority of metabolism occurs in the liver and kidney.

**Excretion**
Less than 1% of terlipressin and <0.1% lysine-vasopressin excreted in urine in healthy volunteers.

While no specific PK study has been conducted with Lucassin in bleeding oesophageal varices, the published literature for terlipressin have been investigated in healthy volunteers and in cirrhotic patients with similar PK characteristics observed in both populations.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**
Terlipressin was not mutagenic or clastogenic in the following tests: *in-vitro* bacterial reverse mutation assay, *in-vivo* mouse micronucleus assay and *in-vitro* mammalian cell (CHO) chromosome aberration assay.

**Carcinogenicity**
Carcinogenicity studies have not been performed with terlipressin.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Mannitol is used as the caking agent. Glacial acetic acid and/or sodium hydroxide are used to adjust the pH to achieve a final product pH of 4.3 - 7.5.

## 6.2 INCOMPATIBILITIES

Terlipressin is incompatible with dextrose solutions.

## 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

Refrigerate LUCASSIN vials at 2-8°C. Vials should be stored in original carton in order to protect from light.
After reconstitution, the solution may be refrigerated (2-8°C) for up to 24 hours before use.
Do not freeze.

## 6.5 NATURE AND CONTENTS OF CONTAINER

LUCASSIN is available as single vials, and also in packs of 12 vials.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical Structure

Terlipressin is a 12-amino acid peptide with the chemical name N-(N- (N-glycylglycyl)glycyl)-8-L-lysinevasopressin.
Terlipressin has the following amino acid sequence:

H-Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-$NH_2$
|_____|

Molecular formula: $C_{52}\ H_{74}\ N_{16}\ O_{15}\ S_2$ (terlipressin free base).
Molecular weight: 1227.4 (terlipressin free base)

**CAS number:** 14636-12-5
**pKa**: 10.01 calculated

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

## 8 SPONSOR

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## 9 DATE OF FIRST APPROVAL

9 January 2012

## 10 DATE OF REVISION

7 June 2018

**Summary Table of Changes**

| Section Changed | Summary of new Information |
|---|---|
| Complete document | Format updated as per TGA Nov 2017 Guidance |
| 4.1 Therapeutic Indications | New indication of bleeding oesophageal varices added |
| 4.2 Dose and method of Administration | Updated sections with information specific to the indication of bleeding oesophageal varices, updated clinical information or post-marketing experience. |
| 4.4 Special Warnings and Precautions for Use | |
| 4.5 Interactions with Other Medicines and Other Forms of Interaction | |
| 4.7 Effects on Ability to Drive or Use machinery | |
| 4.8 Adverse effects (Undesirable effects) | |
| 4.9 Overdose | |
| 5.1 Pharmacodynamic properties (Clinical Trials, Pharmacokinetics) | |

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