Attachment 1: Product information for AusPAR Lucassin Terlipressin Ikaria Australia Pty Ltd Sponsor PM-2010-02975-3-1 Date of finalisation 27 August 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

LUCASSIN®
(Terlipressin 0.85 mg powder for injection)

NAME OF THE MEDICINE:

Terlipressin.

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

DESCRIPTION:

LUCASSIN is provided as a sterile, lyophilized powder in a clear glass vial for intravenous administration; 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. 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.

Each vial must be reconstituted with 5mL of 0.9% sodium chloride injection prior to use.

PHARMACOLOGY:

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 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.

Pharmacokinetics:

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

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), with less than 1% of terlipressin and <0.1% lysine-vasopressin excreted in urine in healthy volunteers. 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.

CLINICAL TRIALS:

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.

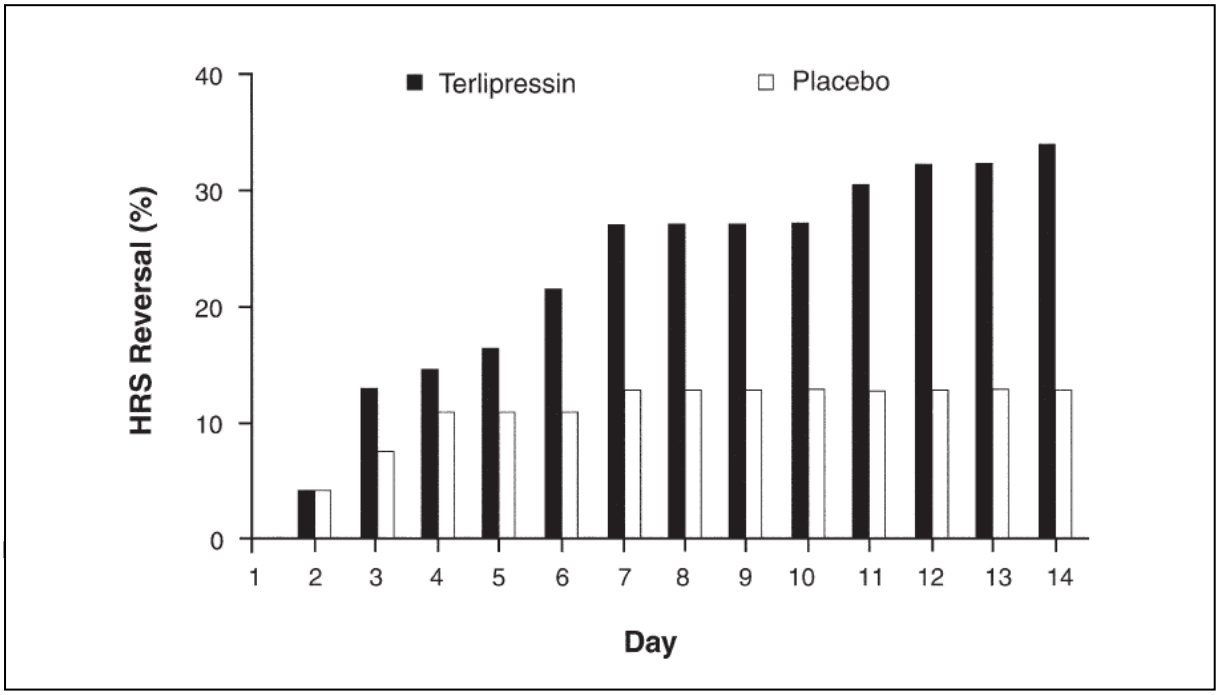
Patients were monitored for up to 180 days after administration of first dose. Primary endpoints included: Treatment success at Day 14 (two serum creatinine [SCr] levels ≤132.6 µmol/L 48 ± 24 h apart without intervening SCr ³ 221 µmol/L, liver transplant or dialysis up to Day 14); HRS reversal on treatment (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 the Table 1. The cumulative incidence of HRS reversal is presented in Figure 1.

Table 1. 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]

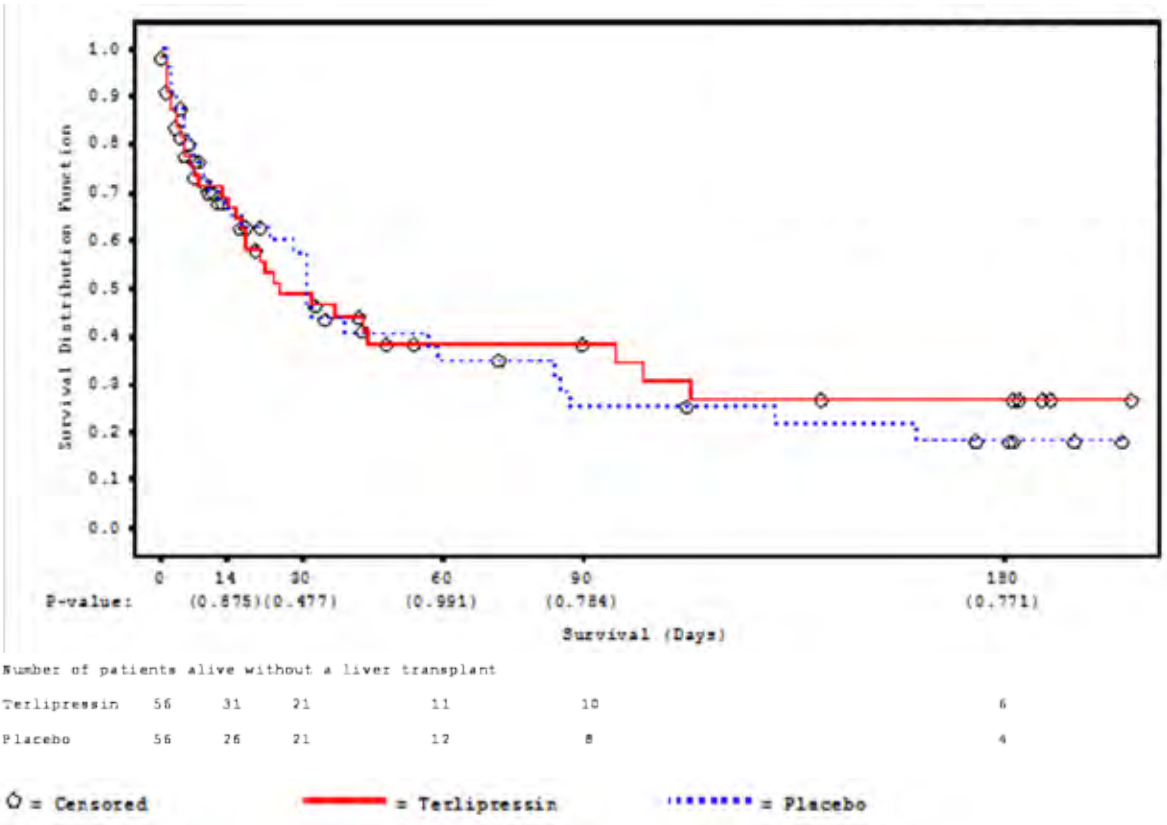
[a]Incorporates additional SCr data collected after initial database closure
[b]From a stratified Cochran-Mantel-Haenszel (CMH) test.
[c]Least Square Mean (SE) for change from baseline to Day 14.
[d]p-value comparing treatment groups, from repeated measures ANOVA.

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.

INDICATIONS:

LUCASSIN is indicated for the treatment of patients with hepatorenal syndrome (HRS) type 1 who are actively being considered for a liver transplant.

CONTRAINDICATIONS:

Hypersensitivity to terlipressin or any of the excipients.

PRECAUTIONS:

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. Torsade de pointes, QT prolongation and ventricular fibrillation have been rarely reported in the post-marketing setting.

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.

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.

Effect 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.

Carcinogenicity:
Carcinogenicity studies have not been performed with terlipressin.

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.

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.

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

Use in Elderly:
Of the total number of patients randomised to receive terlipressin in clinical studies, 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.

Renal and Hepatic Impairment:
Patients with HRS type 1 have significant renal and hepatic 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.

Drug 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.

ADVERSE EFFECTS:

The following adverse reactions are discussed in greater detail in the **PRECAUTIONS** section: cardiovascular effects, ischaemic events and respiratory effects.

Adverse Events

Table 2 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 2. 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 3.

Table 3. 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 4. 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.

Post-marketing Experience

The reports submitted to the WHO database in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances, it cannot be proven that a pharmaceutical product or ingredient is the cause of an event. The following serious and/or clinically significant adverse reactions have been reported during post-approval use of terlipressin, primarily in non-HRS type 1 indications. Since these reactions are reported from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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.

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.

DOSAGE AND ADMINISTRATION:

The recommended starting dose is one vial of LUCASSIN (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 two vials of LUCASSIN (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 **PRECAUTIONS**]. 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 the equivalent of two to three vials of LUCASSIN (1.7 - 2.55 mg terlipressin)/day. The maximum dose studied (TAHRS Study) was the equivalent of two vials of LUCASSIN (1.7 mg terlipressin) every 4 hours.

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 hrs prior to use.

Drug Incompatibilities: Terlipressin is incompatible with dextrose solutions.

OVERDOSAGE:

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.

PRESENTATION:
LUCASSIN is supplied as lyophilized terlipressin powder for injection, single-use vials. Each vial of LUCASSIN contains 0.85 mg terlipressin.

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

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.

NAME AND ADDRESS OF THE SPONSOR:
Ikaria Australia Pty Ltd
695 Burke Road
Hawthorn East VIC 3123

POISON SCHEDULE: Schedule 4 – Prescription only medicine

DATE OF TGA APPROVAL: 9 January 2012

Date of most recent amendment: 6 August 2012

LUCASSIN® is a registered trademark of Ikaria, Inc.