Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Terlipressin

## Proprietary Product Name: Lucassin

## Sponsor: Ikaria Australia Pty Ltd

**August 2013**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AVP | Arginine vasopressin (endogenous vasopressin or ADH) |
| EVH | (E) oesophageal Variceal Haemorrhage |
| FHVP | free hepatic venous pressure |
| HR | Heart rate |
| HVPG | Hepatic venous pressure gradient |
| IEVP | intravascular oesophageal variceal pressure |
| IHC | intrinsic hepatic clearance |
| IVP | Intravariceal pressure |
| HRS | Hepatorenal Syndrome |
| LVP | Lycine-Vasopressin |
| MAP | Mean arterial pressure |
| MELD Score | The Model for End stage Liver Disease (MELD) score is a disease severity scoring system used to rank adult patients waiting for liver transplantation. It is a composite of total bilirubin, INR and SCr. The MELD score numerically ranks patients from 6 (less ill) to 40 (gravely ill). |
| MPBFV | mean portal blood flow velocity |
| PBFV | Portal blood flow velocity |
| PVF or PVBF | Portal venous blood flow |
| SCr or SeCr | Serum Creatinine |
| TdP | Torsades de pointes |
| TGLVP | Triglycylvasopressin (terlipressin) |
| VPG | Variceal pressure gradient |
| VWT | Estimated variceal wall tension |
| WHVP | Wedged hepatic venous pressure |
| WMD | Weighted Mean Differences |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New Chemical Entity |
| *Decision:* | Approved |
| *Date of decision:* | 9 January 2012 |
| *Active ingredient:* | Terlipressin |
| *Product name:* | Lucassin |
| *sponsor's name and address:* | Ikaria Australia Pty Ltd<br>695 Burke Road<br>Hawthorn East Vic 3123 |
| *Dose form:* | Powder for injection |
| *Strength:* | 0.85 mg per vial |
| *Container:* | Type I glass vial fitted with grey bromobutyl rubber stopper and aluminium seal with green plastic flip-off cap. |
| *Pack size(s):* | 1 or 12 vials per carton |
| *Approved Therapeutic use:* | The treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for a liver transplant. |
| *Route of administration:* | Intravenous (IV) |
| *Dosage:* | 0.85 mg terlipressin (free base) every 6 h (starting dose). |
| *ARTG Number:* | 176845 |

## Product background

Hepatorenal syndrome (HRS) is a serious complication of advanced cirrhosis, characterised by renal failure and major disturbances in circulatory function. HRS is at the end of a spectrum of functional renal abnormalities caused by severe vasoconstriction of the renal circulation which leads to a pronounced reduction in glomerular filtration rate. The more common form of HRS is Type 1 (HRS-1), which is characterised by an *abrupt onset* and *rapid progression* of renal dysfunction defined by a doubling of the initial serum creatinine to a level greater than 220 µmol/L in less than 2 weeks. In contrast, Type 2 HRS has a more protracted course, characterised by a slower decline in renal function, often over months. Diagnosis of HRS includes decreased creatinine clearance or elevated serum creatinine and is made after exclusion of other disorders that can cause renal failure in cirrhosis.

It has been estimated that untreated HRS-1 carries a mortality of approximately 80% at 2 weeks, with only 10% of patients surviving more than 3 months.

The key pathophysiological change responsible for the development of HRS in cirrhotic patients with advanced liver dysfunction is the development of arterial vasodilatation. This occurs primarily within the splanchnic circulation and is mediated by the local release of potent vasodilators, of which the most important is nitric oxide. The resultant decrease in systemic vascular resistance and effective circulating blood volume precipitates a chain of sequelae including the reflex secretion of vasoconstrictor hormones such as renin, angiotensin, antidiuretic hormone, catecholamines and endothelin, as well as increased sympathetic nervous system activation. These latter changes lead to renal vasoconstriction, reduced renal perfusion, reduction in glomerular filtration rate and renal failure.

The definitive treatment for HRS-1 is liver transplantation, supported by pharmacotherapy either as bridging treatment to transplantation, or for the management of those patients who are not liver transplant candidates.

Therapeutic Guidelines Gastrointestinal notes that this condition occurs predominantly in patients with advanced cirrhosis and usually in the setting of severe ascites and hyponatraemia and may be precipitated by infection, diuretics, nephrotoxic drugs, gastrointestinal bleeding or large volume paracentesis. It recommends that particular care should be taken to avoid renal impairment in patients at risk for HRS and that initial management involve correction of hypovolaemia and other precipitants and, if renal dysfunction fails to improve, that consideration be given to the use of terlipressin 0.5 to 2 mg intravenously (IV) 6-12 hourly + human albumin 20% 100 mL IV twice daily (bd) both given for 7-14 days. The Guideline then recommends that patients who have had an episode of HRS be considered for liver transplantation.

Lucassin contains terlipressin, which is a systemic vasoconstrictor, via vasopressin $V_1$ receptors, acting both as a prodrug for lysine-vasopressin (LVP) and having pharmacological activity on its own, albeit of lower potency than LVP. The duration of action of terlipressin is longer than vasopressin and is due to cleavage of the N-terminal glycyl residues of terlipressin by various tissue peptidases, resulting in release of the pharmacologically active metabolite LVP.

An expert in the field was given access to the clinical evaluation report (CER) by the sponsor, and independently wrote to the TGA advising that in Australia terlipressin is used as a "bridge to transplant" in patients with HRS. Terlipressin is used in this setting to improve renal function before transplantation as it avoids dialysis and significant renal impairment. It is the current standard of care in patients with HRS. Terlipressin is available under the Special Access Scheme.

This AusPAR describes the evaluation of a submission by Ikaria Australia Pty Ltd (the sponsor) to register Lucassin for treatment of HRS-1.

Proposed dosage is 0.85 mg terlipressin (free base) every 6 hours by slow IV bolus injection. Dose may be increased to 1.7 mg every 6 hours if serum creatinine has not decreased by at least 30% from the baseline value after 3 days. Treatment should be continued until about 2 days after the patient achieves HRS reversal (serum creatinine ≤1.5 mg/dL [that is, ≤132.6 µmol/L]). The maximum duration of treatment is 2 weeks.

## Regulatory status

Lucassin was designated by the TGA as an Orphan Drug on 25 June 2010 for the treatment of patients with hepatorenal syndrome Type 1 (HRS-1) and for the treatment of oesophageal variceal haemorrhage (OVH).

A similar application has been submitted in the US for the proposed indication of hepatorenal syndrome, Type 1 (HRS-1), as an orphan designated, fast tracked, rolling New

Drug Application (NDA) commencing on 27 May 2008. The application is under consideration. There have been no other submissions.

Terlipressin was first approved in the early 1980s in Germany for treatment of patients with oesophageal variceal haemorrhage. Products containing terlipressin have been marketed in Europe, South America and Asia for treatment of oesophageal variceal haemorrhage. Terlipressin is also approved for the treatment of HRS in France, India, Ireland, Mexico, Portugal, South Korea, Taiwan and Spain.

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

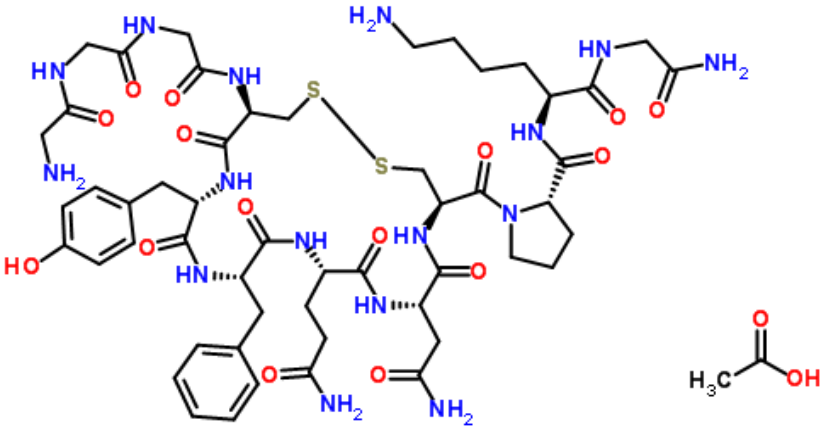
# II. Quality findings

Terlipressin is a synthetic vasopressin analog derived from the natural hormone, lysine-vasopressin (LVP). The substance (structure of the monoacetate reproduced below) is comprised of twelve amino acids each with the L-configuration (except for glycine, which does not have a chiral centre), and in which the C-terminal glycine is amidated. There is a disulfide bridge between $Cys^4$ and $Cys^9$.

**Figure 1. Chemical structure of terlipressin**

H-Gly-Gly-Gly-Cys-Tyr$^5$-Phe-Gln-Asn-Cys-Pro$^{10}$-Lys-Gly-$NH_2$

Free Base



Terlipressin Monoacetate

The substance is manufactured by conventional solid phase peptide synthesis and is isolated nominally as the diacetate pentahydrate salt (but containing a variable amount of acetic acid) by lyophilisation. As such, particle size and polymorphism are not relevant. The drug substance is freely soluble in water.

The drug is presented as a white to off white lyophilised powder in clear, USP Type I glass vials fitted with a grey bromobutyl rubber stopper and aluminium seal with a green plastic

flip-off cap. Each vial contains terlipressin (as the diacetate) equivalent to 0.85 mg of terlipressin "free base".[1]

The specifications applied to the drug substance are satisfactory. The limit applied to the residual trifluoroacetic acid impurity has been reviewed and accepted by Medicines Toxicology Evaluation Section of the TGA.

### Drug product

The product proposed for registration is a sterile, lyophilised powder, presented in clear glass vials for IV administration following reconstitution with 5 mL of sterile 0.9% sodium chloride injection. Each vial of product contains 0.85 mg terlipressin free base and approximately two equivalents (0.084 mg) of acetic acid. The drug substance is present mainly in the form of terlipressin diacetate.

The product (Lucassin) is sterilised by filtration prior to lyophilisation, and contains no antimicrobial preservative.

The finished product specifications were acceptable.

Adequate stability data were provided to support the proposed shelf life of 2 years[2] at 2-8°C stored in the original carton to protect from light. The reconstituted injection was shown to be stable when stored at 2° - 8°C such that the following recommendation is supported: "If not administered immediately, the reconstituted solution should be refrigerated (2 - 8°C) up to 24 hrs prior to use". Terlipressin is incompatible with dextrose solutions. This is reflected in the proposed product information (PI).

Sterility and safety-endotoxins aspects of the submission were evaluated and were acceptable.

### Biopharmaceutics

No bioavailability data are required as the product, after reconstitution, is a simple aqueous solution that is given IV.

### Quality summary and conclusions

There were no objections in respect of chemistry, manufacturing and controls to registration of the powder for injection.

## III. Nonclinical findings

### Introduction

Terlipressin (triglycyl-lycine-vasopressin [LVP]) is a synthetic vasopressin analog that acts on vasopressin receptors, both as a pro-drug for lysine vasopressin (LVP) and probably with pharmacological activity on its own, albeit with lower potency. The endogenous vasopressin is arginine vasopressin (AVP), a nonapeptide with arginine in the 8 position. LVP is a porcine vasopressor peptide with lysine in the 8 position. There are 4 known receptors that bind vasopressin with significant affinity: $V_{1a}$ (vasopressor), $V_{1b}$ (pituitary),

[1] The drug will be referred to as simply terlipressin for the remainder of this AusPAR.
[2] The shelf life of this product has since been extended to 36 months at 2-8°C, protected from light (approved by the TGA on 20 June 2013).

$V_2$ (renal) and OT (oxytocin; uterine). $V_{1a}$ receptors are expressed in the liver, vascular smooth muscle, brain and in many other tissues. In the vasculature, $V_{1a}$ receptors mediate vasoconstriction in response to vasopressin binding. $V_{1b}$ receptors in the anterior pituitary mediate the ACTH releasing effects of AVP while $V_2$ receptors in the collecting duct of the kidney mediate the antidiuretic action of AVP. Oxytocin (OT) receptors are expressed in the uterus, the mammary gland, the ovary and several other tissues. OT receptors mediate the uterine contracting effect of OT. Terlipressin is intended to act at the $V_{1a}$ receptors, mediating vasoconstriction, particularly in the splanchnic area, resulting in an increase in arterial volume, increase in arterial pressure and normalisation of endogenous vasoconstrictor systems resulting in increased renal blood flow and improved renal function.

The nonclinical data consisted of published papers (with terlipressin or LVP) and a small number of sponsor commissioned studies (with terlipressin). A large body of data was submitted to support efficacy in animal models of liver disease but the toxicological dossier was quite limited. While pivotal repeat dose toxicity studies were compliant with Good Laboratory Practice (GLP), the design and conduct of these studies were suboptimal, limiting the value of the findings. Reproductive toxicity studies were restricted to examinations of embryofetal toxicity.

## Pharmacology

### Primary pharmacology

Pharmacology studies examined receptor binding and vasoconstrictor activity (*in vitro* and *in vivo*) of terlipressin and LVP. LVP bound to both the human and rat $V_{1a}$ receptors with similar affinity ($K_i/K_d$ 2.3–8 nM; 2–8 times the clinical plasma level of LVP). No information was provided on binding to dog vasopressin receptors. Terlipressin had some activity at the human $V_{1a}$ receptor in a functional assay, albeit with lower potency than LVP (>100 times). The putative metabolite of terlipressin, monoglycyl-LVP, had similar potency to terlipressin (pressor and antidiuretic activities in rats), while another putative metabolite, diglycyl-LVP, had lower potency. All four compounds had 54–100% the efficacy of AVP at the human $V_{1a}$ receptor as assessed by an *in vitro* functional assay.

Terlipressin had vasoconstrictive activity in isolated systemic and splanchnic vessels from rats and small arteries of the human tubo-ovarian vasculature. The vasoconstrictive activity of terlipressin was less potent than both LVP and AVP. Terlipressin (≥30 nM; ~0.6 times the clinical maximum plasma concentration [$C_{max}$] of terlipressin) decreased the coronary blood flow and impaired myocardial performances of an isolated rabbit heart. These cardiac effects were significantly reduced on hearts pre-treated with a selective $V_{1a}$ receptor antagonist, confirming the vasoconstrictive activity occurred through this receptor.

The chosen models of liver disease were rats with induced portal hypertension or cirrhosis. These are generally considered acceptable models for end stage liver disease. Dysfunction of the splanchnic circulation resembles that in patients with late stage liver disease and changes in handling of sodium and water by the kidney are similar to those observed in HRS patients. In these models, terlipressin decreased portal vein pressure and superior mesenteric arterial blood flow, increased mean arterial pressure and total peripheral resistance. A cardiodepressant effect (decreased heart rate and cardiac output) was also seen. Terlipressin redirected blood flow from the gut and skin (and other organs) to the kidneys. The median effective dose ($ED_{50}$) was determined to be 12.3 mg/kg based on mean arterial pressure; estimated $C_{max}$ 28.9 ng/mL[3], 0.5 times the clinical Cmax. The

[3] Estimated from data in Study CB06-5013-R-TX where a $C_{5\ min}$ of 352 ng/mL was seen with a 150 µg/kg dose.

onset of pressor responses to terlipressin appeared to be more rapid (immediate) than accounted for by LVP formation, suggesting that terlipressin contributed, at least initially, to the pressor response. Terlipressin was less potent than AVP and LVP in increasing blood pressure. With terlipressin, maximal activity was delayed and the duration of action was longer. The pressor activity of monoglycyl-LVP and diglycyl-LVP showed a similar profile to that of terlipressin. The vasopressor activity was similar in rats and dogs. As the animal studies were acute, normalisation of endogenous vasoconstrictor systems and improvement in renal function were not assessed.

Terlipressin given during haemorrhage was less effective than when given during a stable state in experimental portal hypertension or cirrhosis. This splanchnic hyporesponse was associated with an overexpression of constitutive nitric oxide synthase and cyclooxygenase-1 in the superior mesenteric artery and increased glucagon release due to blood retention in the stomach. While the splanchnic response was diminished during haemorrhage, the systemic responses to terlipressin (increased mean arterial pressure and decreased cardiac output) were retained.

Overall, the animal pharmacology data presented by the sponsor suggested that terlipressin reduces blood flow to the skin, stomach and small intestine, while increasing flow to the liver and kidney. The delay in onset and long duration of action supports the proposed dosage regimen of a bolus IV injection every 6 hours (h), rather than a continuous infusion that would be required for the LVP metabolite. LVP had similar affinity at rat and human $V_{1a}$ receptors and had similar vasopressor activity in rats and dogs, supporting the use of these animal models in the toxicity studies.

### Secondary pharmacodynamics

The binding of terlipressin or LVP to other receptors was not extensively studied. LVP had similar binding affinity at the human $V_{1b}$, $V_2$ and $V_{1a}$ receptors but less binding affinity at the human oxytocin receptor ($K_i$ 25 nM). The binding affinity of LVP was approximately half that of AVP at all receptors. LVP had similar affinity at the rat $V_{1a}$, $V_{1b}$, $V_2$ and oxytocin receptors ($K_D$ 1.7–8 nM). In rats, LVP had similar pressor ($V_{1a}$) and antidiuretic ($V_2$) activity, with 27 times lower oxytocin activity. Terlipressin had similar pressor and antidiuretic activity in one rat study but twice the pressor activity relative to the antidiuretic activity in another study. A dose dependent antidiuretic effect was seen at 0.05–1 µg/kg subcutaneous (SC) terlipressin in rats but marked natriuresis was seen at 5–20 µg/kg SC terlipressin (estimated $C_{max}$ 12 ng/mL at 5 µg/kg; 0.2 times the clinical $C_{max}$). In dogs, the antidiuretic activity of LVP was ~15% that of AVP but similar pressor activity to that seen in rats, suggesting a difference in sensitivity of the $V_2$ receptor in this species. This is not unusual as species-specific differences in susceptibility at the $V_2$ receptor are known (Manning *et al.*, 2008).[4] At the proposed clinical dose, the pressor effects of terlipressin (and/or its metabolite LVP) are likely to predominate over the antidiuretic effect to increase renal perfusion.

### Safety pharmacology

Specialised safety pharmacology studies were not conducted but effects on the central nervous, cardiovascular, gastrointestinal, renal and respiratory systems were investigated in toxicity and pharmacology studies. Clinical signs generally indicative of central nervous

[4] Manning M, Stoev S, Chini B, Durroux T, Mouillac B, Guillon G. Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin $V_{1a}$, $V_{1b}$, $V_2$ and OT receptors: research tools and potential therapeutic agents. Prog Brain Res 2008; 170: Chapter 37.
[4] Manning M, Stoev S, Chini B, Durroux T, Mouillac B, Guillon G. Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin $V_{1a}$, $V_{1b}$, $V_2$ and OT receptors: research tools and potential therapeutic agents. Prog Brain Res 2008; 170: Chapter 37.

system (CNS) toxicity were seen in mice, rats and dogs. These included lethargy (≥20 mg/kg IV in mice, ≥0.15 mg/kg IV in rats, ≥0.031 mg/kg IV in dogs), piloerection (≥500 mg/kg IV in mice), ataxia and mobility problems (≥1.5 mg/kg IV in rats, ≥0.15 mg/kg IV in dogs). These clinical signs were transient, lasting up to 60 minutes (min) post-dose, consistent with the exposure to terlipressin and are probably related to its vasoconstrictor activity. A No Observable Effect Level (NOEL) was not established but, as lethargy occurred at approximately the clinical Cmax (in dogs), some of these effects may be seen clinically.

In pharmacology studies, terlipressin decreased coronary blood flow, increased mean arterial pressure, increased total peripheral resistance, decreased heart rate and reduced the cardiac index, consistent with its pharmacology on $V_{1a}$ receptors in the smooth muscle vasculature. In a 28 day repeat dose toxicity study, there was a slight increase in the QT(c) interval in male dogs treated with 0.125 mg/kg IV twice daily (bd) terlipressin. There was no evidence of QT prolongation in treated females. These findings are difficult to interpret as electrocardiogram (ECG) recordings were conducted >16 h post-dose in males and >3 h post-dose in treated females and plasma levels of terlipressin and LVP would have been low to negligible at these times. Therefore no firm conclusions can be drawn from these data. Based on the known pharmacology of the drug, some cardiovascular findings would be expected clinically.

Intraperitoneal (IP) injections of terlipressin (≥0.1 mg/kg; NOEL 0.05 mg/kg, estimated exposure ratio at Cmax [ERCmax] 2) to rats had a gastroparetic effect, reducing the phasic motility of the stomach. This started 3−10 min post-dose and lasted up to 90 min, consistent with the duration of exposure to pharmacologically active material. Vomiting and defaecation were seen in dogs treated with ≥0.031 mg/kg IV bd (ERCmax 1.3; NOEL not established). The clinical signs of gastrointestinal disturbance abated within 1 h post-dose and are consistent with the vasoconstrictive action of terlipressin and LVP on the smooth muscle vasculature. These findings suggest that some gastrointestinal disturbances may be expected in the clinical setting.

SC administration of terlipressin (0.05−1 mg/kg) to rats had a dose dependent antidiuretic effect. The antidiuretic effect of terlipressin was slower and more sustained than LVP, probably due to the conversion of terlipressin to LVP. The antidiuretic activities of terlipressin and LVP were 2.2−3.3 U/mg and 284 U/mg, respectively, in rats. The antidiuretic potency of terlipressin and LVP was approximately equivalent to their pressor potency in this species. In dogs, however, LVP was less potent in the $V_2$ mediated antidiuretic activity than the $V_{1a}$ mediated pressor activity. However, at the proposed clinical dose, the pressor effects are likely to predominate over the antidiuretic effect (see *Secondary pharmacodynamics*).Immediately after terlipressin administration, laboured and heavy breathing were seen in rats (≥0.15 mg/kg IV, estimated ERCmax6; NOEL not established) and dogs (≥0.125 mg/kg IV; ERCmax 3 at the NOEL). These respiratory difficulties lasted for the duration of exposure to pharmacologically active material and are consistent with vasoconstrictive activity on smooth muscle.

### Pharmacodynamic drug interactions

The sponsor submitted a number of published papers describing the effects of terlipressin combined with other drugs in portal hypertensive or cirrhotic rats. Octreotide and β-blockers are frequently administered to patients with cirrhosis. The α- and β-adrenoceptor agonist, dobutamine, and the α-adrenoceptor antagonist, DL-028, reduced the systemic pressor effects of terlipressin. The combination of terlipressin and the β-adrenoceptor antagonist, propranolol, produced a greater reduction in portal pressure in portal hypertensive rats, than terlipressin alone. This combinatory effect was not seen in cirrhotic rats. The effect of octreotide in portal hypertensive rats was mixed, depending on the order of administration. Administration of octreotide to portal hypertensive rats 15

min after terlipressin appeared to attenuate the effects of terlipressin, while the reverse order had no significant effect. Alkaloid vasodilators had varying effects on the splanchnic response to terlipressin. Tetramethylpyrazine enhanced the portal hypotensive effects of terlipressin but reduced the systemic pressor and cardiodepressant effects. Whereas tetrandine, when co-administered with terlipressin attenuated both the splanchnic and systemic effects of terlipressin in portal hypertensive rats.

### Pharmacokinetics

Pharmacokinetic studies with terlipressin were limited. Plasma kinetic profiles were assessed in repeat dose toxicity studies but technical problems limited the usefulness of the acquired information. The severe vasoconstrictive activity of terlipressin impeded blood sampling in the first 2 h post-dose in rats, although adequate data could be obtained. Following IV administration, plasma terlipressin levels fell rapidly in rats, with an elimination half-life of 0.09–0.22 h. The fall in terlipressin levels coincided with an increase in LVP concentration, peaking at 5–10 min and falling below the limit of detection by 1 h post-dose. Results in the dog study are of questionable reliability due to reported sample mislabelling and discrepancies in the time of blood collection. Furthermore, terlipressin levels were unexplainably high in a number of pre-dose samples. Blood samples from the control group were not collected and assayed, as recommended in the TGA-adopted EU guideline, so contamination of blood samples cannot be dismissed and the validity of the results is not assured.[5] It is noted that, with chronic administration to dogs, terlipressin levels fell below the level of detection 1 h post-dose. The fall in terlipressin levels coincided with an increase in LVP levels, as expected. However, a second peak of terlipressin occurred 2–4 h post-dose, after LVP levels fell below the limit of detection. The second terlipressin peak is difficult to explain. A reformation of terlipressin from LVP is unlikely and terlipressin is unlikely to undergo enterohepatic recirculation intact. Due to the questionable reliability of the plasma concentration data, limited quantitative information can be gained from the dog study. Nonetheless, qualitatively, the plasma kinetic profile in dogs was similar to that in rats and humans; the elimination half-lives for terlipressin and LVP were short and the plasma kinetic profile of terlipressin and LVP in humans support the proposed 4 times daily dosage regimen to achieve sustained vasoconstrictive activity.

Following IV administration of [$^{3}$H-Tyr]-LVP to rats, radioactivity was widely distributed with the kidney, liver, small intestine, neurohypophysis, adenohypophysis having appreciable levels of radioactivity, 1 h post-dose. The radioactivity in the kidneys, liver and small intestine was attributed to the degradation product $^{3}$H-tyrosine, consistent with these organs having high metabolic activity on terlipressin. Radioactivity in the neurohypophysis and adenohypophysis are consistent with the presence of vasopressin receptors in these tissues.

*In vitro* studies indicated that, in rats, terlipressin is metabolised by various tissues, including the liver, kidney and heart. Significant metabolism of terlipressin was also observed in homogenates of human liver and myometrial tissues. Subcellular fractionation studies indicated the majority of the metabolic activity in these tissues was associated with the cytosolic and mitochondrial fractions and limited activity was associated with the microsomal fraction. Metabolism of terlipressin is likely to involve peptidases, initially to form LVP, then cleavage of the C-terminal glycine amino group, with subsequent degradation. There was no evidence of metabolism of terlipressin in fresh human plasma,

[5] EMEA, Committee for Medicinal Products for Human Use (CHMP), 17 March 2005. Guideline on the Evaluation of Control Samples in Nonclinical Safety Studies: Checking for Contamination with the Test Substance, CPMP/SWP/1094/04.[6] Forsling ML, Aziz LA, Miller M, Davies R, Donovan B. Conversion of triglycylvasopressin to lysine-vasopressin in man. J Endocr 1980; 85: 237-244.

erythrocytes or whole blood and serum. The metabolism of terlipressin is likely to be similar in animals and humans.

Only 2–8% of the administered terlipressin was excreted in the urine of cats. In rats that received LVP, only 0.5% of the administered drug was excreted intact. The low level of urinary excretion in animals is consistent with findings in humans where <1% of the injected material is excreted in urine (Forsling *et al.*, 1980).[6] These data confirm the extensive role of metabolism in the clearance of terlipressin.

### Pharmacokinetic drug interactions

In *in vitro* assays, there was no significant inhibition or induction of the human cytochrome P450 (CYP) isozymes, CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4 or inhibition of CYP2C8 at terlipressin concentrations up to 5000 ng/mL (~80 times the clinical plasma concentration at 5 min [C5 min]). As terlipressin is not appreciably metabolised by CYP450 enzymes, drug interactions involving CYP450 enzymes are unlikely.

## Toxicology

### General toxicity

#### *Single dose toxicity*

Dedicated single dose toxicity studies were not conducted but single dose ranging studies were conducted prior to the mouse micronucleus study and the 7 day repeat dose toxicity studies in rats and dogs. As such, the observation period post-dose was only 3 days, rather than the 14 days recommended in the TGA-adopted EU guideline.[7] This is not a particular concern as a recovery period was included in the repeat dose toxicity studies. Mortalities in the mouse and rat studies occurred within 60 min of dosing and with perimortem bleeding observed, are likely to be due to severe vasoconstriction. Clinical signs of lethargy, dyspnoea, ataxia and open mouth gasping were observed in all species, starting immediately after dosing and lasting for ~1 h. These clinical signs were most likely a result, either directly or secondary, of the cardiovascular effects of terlipressin (increased peripheral resistance, decreased heart rate, decreased cardiac output, decreased coronary blood flow and decreased skin blood flow). Vomiting and defaecation observed in dogs at ≥0.15 mg/kg IV terlipressin are consistent with the pharmacological action on the gastrointestinal tract. Maximum non-lethal doses were 20 mg/kg IV in mice (60 mg/m2), <2 mg/kg IV in rats (12 mg/m2) and 0.5 mg/kg IV in dogs (10 mg/m2; >7 times the maximum clinical dose of 2 mg [1.3 mg/m2]). Gross pathological analyses were only conducted in rats, where the kidneys and lungs appeared to be target organs. Renal and pulmonary findings were also seen in the repeat dose toxicity studies and therefore are discussed below.

#### *Repeat dose toxicity*

Repeat dose toxicity studies of up to 28 days duration were conducted in rats and dogs. All studies were conducted under GLP conditions. Adequate animal numbers of both sexes were used. The pivotal 28 day studies included a 14 day recovery period to assess the reversibility of toxicity findings. The duration of the repeat dose toxicity studies is not generally considered adequate to support the proposed clinical use of 14 days. Studies of

[6] Forsling ML, Aziz LA, Miller M, Davies R, Donovan B. Conversion of triglycylvasopressin to lysine-vasopressin in man. J Endocr 1980; 85: 237-244.
[7] pp. 3 - 8 of the Rules Governing Medicinal Products in the European Union - EudraLex - Medicinal products for human use, 1998 Edition: Volume 3B - Safety and the Environment - 3BS1a. Single Dose Toxicity.

at least 3–6 months duration would normally be required to support the clinical use of up to 1 month for the treatment of life-threatening conditions.[8,9] Therefore, the short duration of studies may not have revealed the full toxicological profile of terlipressin.

Toxicokinetic data were collected in both pivotal studies. Dosing in the rat study was once daily and animals were only exposed to pharmacologically active drug related material for 1 h per day. This does not fully replicate the clinical situation where HRS patients are expected to be continuously exposed to pharmacologically active material (terlipressin and LVP) with the proposed 4 times daily dosing regimen. Daily exposures (based on the area under the plasma concentration time curve [AUC]) were also low compared with the anticipated clinical exposure at the 1 mg/6 h clinical dose (Table 1); AUC data were not available for the maximum recommended human dose (MRHD) (2 mg/6 h) but animal/human exposure ratios would have been even lower at this clinical dose. Higher doses with the single dose regimen in rats would not have been feasible due to the high mortality rate (immediately after dosing) observed at the highest tested dose. However, as mortalities were observed immediately after dosing and were associated with high $C_{max}$ values, greater exposure (AUC) could have been achieved by more frequent dosing, either twice or three times daily, a regimen more comparable with proposed clinical dosing. Due to the short daily duration of exposure to pharmacologically-active material, and the low overall exposures achieved, the full toxicological profile of terlipressin is unlikely to have been revealed in the submitted rat studies. Relative exposures are shown in Table 1.

**Table 1.Relative exposures of terlipressin and LVP achieved in repeat dose toxicity studies**

| Species (Strain) | Study | Dose (mg/kg/day) IV | Terlipressin | | | | LVP | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $AUC_{0-24h}$ (ng·h/mL) | $C_{5\ min}$ (ng/mL) | $ER_{AUC}$ | $ER_{C5min}$ | $AUC_{0-24h}$ (ng·h/mL) | $C_{max}$ (ng/mL) | $ER_{AUC}$ | $ER_{Cmax}$ |
| **Rat** (SD) | CB06-5013-R-TX | 0.15 | 51 | 352 | 0.3 | 5.7 | 1.9 | 9.3 | 0.2 | 8 |
| | | 0.5 | 246 | 1078 | 1.5 | 17 | 16 | 22 | 1.6 | 20 |
| | | 1.5 | 830 | 5385 | 5 | 87 | 54 | 75 | 5 | 68 |
| **Human** | OT-0401 | 1 mg every 6 h | 162 | 62 | – | – | 10 | 1.1 | – | – |

ER, animal/human exposure ratio

In the study in dogs, twice daily dosing was used and the duration of exposure to pharmacologically active material might be considered adequate to support the proposed clinical dosage regimen. However, some concerns with the conduct of the toxicokinetic portion of the study limit the value of the information gained (see above) and continuous exposure to pharmacologically active material cannot be verified. As exposure comparisons could not be made confidently based on AUC data, dose comparisons based on body surface area (BSA) were made for this species (Table 2). Doses used were generally low compared with clinical dosing at 1 mg every 6 h, and subclinical compared with the MRHD (2 mg every 6 h). Therefore, the full toxicological profile is unlikely to have been revealed in the submitted dog studies.

[8] EMEA, ICH Topic S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, November 2009. Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008).
[9] EMEA, Committee for Proprietary Medicinal Products (CPMP), May 1999. ICH Topic S4. Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing), CPMP/ICH/300/95.

**Table 1. Relative dose of terlipressin used in repeat dose toxicity studies**

| Species (Strain) | Study | Dose (mg/kg/day) IV | Dose (mg/m2/day)*a* | Relative dose based on BSA |
|---|---|---|---|---|
| **Rat** (SD) | CB06-5013-R-TX | 0.15 | 0.9 | 0.4 |
| | | 0.5 | 3 | 1.4 |
| | | 1.5 | 9 | 4 |
| **Dog** (Beagle) | CB06-5030-D-TX | 0.15 bd | 6 | 2.7 |
| | CB06-5089-D-TX | 0.031 bd | 1.2 | 0.5 |
| | | 0.0625 bd | 2.5 | 1.1 |
| | | 0.125 bd | 5 | 2.3 |
| **Human** | OT-0401 | 1 mg every 6 h*b* | 2.2 | – |

[a]Using mg/kg to mg/m2 conversion factors of 6, 20 and 33 for rats, dogs and humans, respectively;
[b]corresponds to 0.85 mg terlipressin every 6 h

Despite the flaws in the design and conduct of the submitted toxicity studies, some drug related effects were seen and were largely associated with pharmacological activity. Male rats appeared to be more sensitive to the vasoconstrictive properties of terlipressin, based on mortalities. Deaths occurred at ≥0.5 mg/kg/day in males and 1.5 mg/kg/day in females. Most deaths occurred following the first dose, generally within the first hour. The cause of death was attributed to pulmonary oedema and/or haemorrhage due to reduced perfusion associated with pharmacological action. No mortalities were observed in the dog studies.

The kidney was a target organ in both rats and dogs. Trace to moderate nephritis was seen in rats treated with ≥0.5 mg/kg/day IV terlipressin (NOEL 0.15 mg/kg/day; exposure ratio based on AUC [ERAUC] 0.3) and dogs treated with ≥0.031 mg/kg bd (NOEL not established). Mild to severe renal tubular nephrosis with interstitial inflammation and fibrosis, probably ischaemic in origin, was seen in rats treated with 2 mg/kg/day IV terlipressin for 7 days. Mild lymphocytic infiltration was seen in dogs treated with ≥0.031 mg/kg bd IV terlipressin. These kidney lesions are likely associated with the pharmacological activity and they showed a trend to reversion after a 2 week treatment free recovery period.

Mild to moderate pulmonary inflammation was observed in dogs treated with ≥0.031 mg/kg bd IV (0.5 times the clinical dose based on BSA). This was suggested by the sponsor to be secondary to the pharmacological action of terlipressin – a result of a temporary reduction in blood flow caused by the vasoconstrictor activity of terlipressin followed by a subsequent reperfusion. No inflammation or other pulmonary changes were observed after a 2 week treatment free period, indicating the changes were reversible. While there was no evidence of fibrosis in the study, the duration of the study (1 month) is likely to be too short for fibrosis to develop.

Reduced testicular weights and mild to moderate seminiferous tubular degeneration was observed in male rats treated with ≥0.5 mg/kg/day IV terlipressin (ERAUC 0.3 at the NOEL). This could be due to a direct vasoconstrictor effect on the testes, resulting in

reduced blood flow, ischaemia and tubular degeneration and/or a direct effect on V1a receptors in Leydig cells.

Skin pallor was seen in rats treated with ≥0.15 mg/kg/day IV. This is consistent with reduced cutaneous blood flow, a pharmacological effect of terlipressin. Enlarged adrenal glands were also seen in rats treated with ≥0.15 mg/kg/day IV terlipressin but without any corresponding microscopic changes. This could be due to a pharmacological effect, with terlipressin increasing adrenocorticotropic hormone (ACTH) levels by acting on the pituitary V1b receptors. Trace to mild cortical lymphoid depletion was seen in the thymus of female rats treated with ≥0.5 mg/kg/day IV terlipressin. The clinical relevance of this is not known. Due to the short duration of daily exposure, some toxicological findings that may be expected as a result of prolonged vasoconstriction (ischaemic events in cardiac and gastrointestinal tissues and in the skin) were not seen in the toxicity studies. These events are possible during clinical use of terlipressin.

The sponsor noted that the intended clinical treatment is for a maximum period of 2 weeks and that according to the TGA-adopted EU guideline[10], for indications with a treatment duration of up to 2 weeks, 28 day repeat dose toxicity studies are acceptable.

However, the doses, exposures (based on AUC) and daily duration of exposure were all still considered too low to have adequately revealed the toxicological profile of terlipressin. The sponsor acknowledged that the clinical safety profile identified ischaemic events in cardiac, gastrointestinal and skin tissues, which would be associated with prolonged vasoconstriction, as potential risks. As these were not seen in the submitted toxicity studies, it confirms the inadequacy of the repeat dose studies to reveal the full toxicological profile of terlipressin.

### Genotoxicity and carcinogenicity

The genotoxic potential of terlipressin was assessed in the standard battery of tests. Appropriate strains were used in the Ames test. Appropriate concentrations were used in the *in vitro* assays, with high doses used in the mouse micronucleus assay. All assays were appropriately validated. Although toxicokinetic data were not collected in the micronucleus test, clinical signs of toxicity confirmed the animals were adequately exposed. All assays returned negative results, which is to be expected for a peptide like terlipressin. No carcinogenicity studies were submitted. This is considered acceptable given the life threatening condition of the intended patient population, the negative genotoxicity results, and the anticipated short duration of clinical treatment.

### Reproductive toxicity

No studies were submitted to assess the effect of terlipressin on male or female fertility. In repeat dose toxicity studies, reduced testicular weights and mild to moderate seminiferous tubular degeneration were seen in rats treated with ≥0.5 mg/kg/day terlipressin (ERAUC 0.3 at the NOEL) but no sperm analysis was conducted. These testicular effects could be the result of decreased blood flow and/or a direct effect on $V_{1a}$ receptors in Leydig cells (Meidan and Hsueh, 1985).[11] After 14 days without treatment, a trend to reversion was seen. Taken together, some effects on male fertility may be expected with terlipressin treatment. No data were provided on the effects of terlipressin on female fertility. In response to a question, the sponsor noted that in the target patient population, both male and female patients with cirrhosis and end stage liver disease are

[10] ICH Topic M3 (R2), Note For Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (CPMP/ICH/286/95).
[11] Meidan R, Hsueh AJW. Identification and characterisation of arginine vasopressin receptors in the rat testis. Endocrin 1985; 116: 416-423.

recognised as already having a high baseline incidence of infertility as a result of hypothalamic-pituitary-gonadal dysfunction.

No embryofetal toxicity studies were conducted with terlipressin. The sponsor relied on published papers on embryofetal effects with LVP and AVP. Intramuscular injections of LVP (7 mg/kg) to pregnant rabbits from gestation day (GD)8 to GD11 had no significant effect on pregnancy and parturition. However, a single injection on GD20 resulted in a higher incidence of necrotic young and a greater incidence of abortion and vaginal bleeding. After a single injection of LVP on GD28, approximately 4 days before expected parturition, fetuses were dead within 1 h of the injection. Sites of blood accumulation were grossly visible in the placentas with microscopic evidence of focal dilatation and engorgement of maternal labyrinthine tubules with masses of erythrocytes. These findings were attributed to reduced blood flow to the uterus and placenta, resulting in ischaemic events that cause deterioration of tissues, as well as increased uterine contractions. Oxytocin receptor expression is up-regulated just prior to parturition (starting from GD28 in rabbits; Hinko and Soloff, 1992) and abortions have been reported in pregnant rabbits having elevated plasma oxytocin levels and increased uterine activity (Fuchs and Dawood, 1981).[12,13] LVP has some affinity at the oxytocin receptor and therefore these effects could be attributed to $V_{1a}$ or oxytocin receptor activity. Intra-amniotic injection of vasopressin (assumed to be AVP) on GD15 in rats resulted in an increased incidence of dysmelia (Love and Vickers, 1973).[14] These malformations of the digits are likely due to local hypoxia possibly associated with reduced blood flow to the fetus. Maternal injection of vasopressin (assumed to be AVP) on GD17 in rats caused transient hypoxia, bradycardia and serum ion changes in fetuses (Chernoff and Grabowski, 1971).[15] Reduced blood flow to the uterus and placenta was seen in guinea pigs following administration of terlipressin (3–10 mg/kg IV). Clinically, terlipressin has also been reported to increase uterine activity and reduce endometrial blood flow (Laudanski and Akerlund, 1980).[16] Therefore, the adverse embryofetal effects reported for LVP and AVP indicate a risk to fetal development during the clinical use of terlipressin. Given the malformations observed in rat studies with vasopressin analogues, Pregnancy Category D, as chosen by the sponsor, was considered appropriate.

No studies examined the excretion of terlipressin or its metabolite, LVP, in milk, or their effects on breastfed young.

### Local tolerance

Injection site reactions were monitored as endpoints in repeat dose toxicity studies. Perivascular inflammation, ranging in severity from trace to severe was seen in rats treated with ≥0.15 mg/kg IV terlipressin. The incidence and severity of this inflammatory response did not have a clear relationship with dose. Mild to moderate perivascular inflammation was also noted in dogs at 0.124 mg/kg IV, while some inflammation was seen in single animals at lower doses, as well as in the control group. The incidence of haemorrhage was variable in the dog study but all males treated with ≥0.0625 mg/kg bd IV (similar to the maximum clinical dose on a mg/kg basis) all had moderate to severe haemorrhage at the injection site. Oedema was noted in a single male dog treated with

[12] Hinko A, Soloff MS. Characterisation of oxytocin receptors in rabbit amnion involved in the production of prostaglandin E2. *Endocrin* 1992; 130: 3547-3553.
[13] Fuchs, A-R, Dawood, YM. Oxytocin release and uterine activation during parturition in rabbits. *Endocrin* 1981; 107: 1117-1126.
[14] Love AM, Vickers TH. Vasopressin induced dysmelia in rats and its relation to amniocentesis dysmelia. *Br J Exp Path* 1973; 54: 291-297.
[15] Chernoff N, Grabowski CT. Responses of the rat foetus to maternal injections of adrenaline and vasopressin. Br J Pharmacol 1971; 43: 270-278.
[16] Laudanski T, Akerlund M. Uterine effects of N-alpha-triglycyl-(8-lysine)-vasopressin and 8-lysine-vasopressin in the first trimester of pregnancy. *Contraception* 1980; 22: 199-208.

0.125 mg/kg bd IV. Haemorrhage and oedema are consistent with the pharmacological activity of terlipressin. All injection site reactions reversed after a 2 week treatment free period.

No significant haemolysis of human blood was observed at terlipressin concentrations up to 170 ng/mL (~2.7 times the clinical $C_{max}$ of a 1 mg dose).

### Immunogenicity

The immunogenicity of terlipressin was not assessed in animal studies. No anti-terlipressin antibodies were detected in plasma samples taken from 32 HRS-1 patients who had received terlipressin. Given the small size of terlipressin (12 amino acids) the risk of antibody production is low.

### Impurities

The proposed specifications for impurities in the drug substance and degradants in the drug product are either below the ICH qualification thresholds or have been adequately qualified.[17]

## Nonclinical summary and conclusions

Nonclinical data consisted of published papers and a small number of sponsor commissioned studies. The pharmacology of terlipressin was extensively studied but the overall toxicological component of the dossier was considered inadequate.

Terlipressin is a synthetic vasopressin analogue that acts on vasopressin receptors both as a pro-drug for lysine vasopressin (LVP) and with pharmacological activity on its own. Terlipressin had agonistic activity at the human $V_{1a}$ receptor, but with >100 times lower potency than LVP. In animal models of liver disease, terlipressin decreased portal vein pressure and superior mesenteric arterial blow flow, increased mean arterial pressure and total peripheral resistance. A cardiodepressant effect was also seen. The delay in onset and long duration of action supports the proposed clinical dosage regimen. A splanchnic hyporesponse, with retention of the systemic effects, was seen during haemorrhage in experimental liver disease models.

LVP had similar binding affinity at the human $V_{1a}$ (pressor), $V_{1b}$ (pituitary) and $V_2$ (antidiuretic) receptors, but less binding affinity at the human oxytocin receptor. During clinical use, some binding to these receptors is possible but the animal studies indicate the pressor effects of terlipressin (and/or its metabolite LVP) are likely to predominate over the antidiuretic effect, to increase renal perfusion.

Specialised safety pharmacology studies were not conducted, but effects on the CNS, cardiovascular, gastrointestinal (GI), renal and respiratory systems were reported in toxicity and pharmacology studies. The majority of findings can be attributed to the pharmacological action of terlipressin or LVP; lethargy, ataxia and mobility problems; decreased coronary blood flow, decreased heart rate and reduced cardiac output; a gastroparetic effect; an antidiuretic effect at low doses but marked natriuresis at higher doses; laboured and heavy breathing. These effects lasted for the duration of exposure to pharmacologically active material. Effects on ECG parameters were not been adequately assessed.

In summary, the submitted animal pharmacology studies indicated that terlipressin reduced blood flow to the skin, stomach and small intestine, and increased the flow to the

[17] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

liver and kidney, thus supporting the proposed indication. However, as the animal studies were acute, normalisation of endogenous vasoconstrictor systems and improvement in renal function were not assessed.

When used in combination with terlipressin, the α- and β-adrenoceptor agonist, dobutamine, and the α-adrenoceptor antagonist, DL-028, reduced the systemic pressor effects of terlipressin in rat models of liver disease. The combination of terlipressin and the β-adrenoceptor antagonist, propranolol, produced a greater reduction in portal pressure in rats with portal hypertension, but not cirrhosis. Alkaloid vasodilators and octreotide had mixed effects on the splanchnic response to terlipressin.

Pharmacokinetic studies with terlipressin were limited. Qualitatively, the plasma kinetic profile was similar in animals and humans with elimination half-lives for terlipressin and LVP being relatively short. Tissue distribution of radioactivity was widespread following administration of [$^{3}$H-Tyr]-LVP to rats. Terlipressin was extensively metabolised by peptidases in tissues. Less than 10% of the administered drug was excreted intact in urine. Pharmacokinetic drug interactions involving CYP450 enzymes are unlikely.

The toxicological dossier was limited. Single dose toxicity studies were conducted as dose ranging studies for the mouse micronucleus study and repeat dose toxicity studies. The maximum non-lethal doses were 20 mg/kg IV in mice, <2 mg/kg IV in rats and 0.5 mg/kg IV in dogs; >7 times the 2 mg clinical dose on a body surface area basis. Deaths were attributed to severe vasoconstriction, a pharmacological effect.

Repeat dose toxicity studies of 28 days duration were conducted in rats and dogs. Due to inadequacies in study design (short duration, the relatively low doses used, brief daily exposure [1 h in the rat studies compared with the intended 24 h clinical exposure]), the full toxicological profile of terlipressin is unlikely to have been revealed. Nonetheless, toxicity findings were seen in the kidneys, lungs and testes, which can all be attributed to the pressor activity of terlipressin. All of the findings showed a trend to reversion following a 2 week treatment free recovery period.

Terlipressin was not genotoxic in the standard battery of tests. No carcinogenicity studies were submitted, which is considered acceptable given the short duration of use and the negative genotoxicity findings.

No studies were submitted to assess the effect of terlipressin on male or female fertility. Testicular changes in rats treated with ≥0.5 mg/kg/day IV terlipressin suggest some effects on male fertility may be expected with terlipressin treatment. The exposure (AUC) ratio at the NOEL was 0.3. Assessment of embryofetal toxicity relied on published papers with vasopressins. Gestational administration of LVP or arginine vasopressin caused reduced blood flow to the placenta and increased uterine contractions resulting in abortions in pregnant rabbits and limb malformations in rat fetuses. No studies examined the excretion of terlipressin or LVP in milk, or its effects on breastfed young.

Treatment related reactions were observed at the injection sites of rats and dogs. Trace to severe perivascular inflammation was seen at >0.12 mg/kg IV (3 times the 2 mg clinical dose on a mg/kg basis), with haemorrhage seen in male dogs treated with ≥0.0625 mg/kg IV (similar to the maximum clinical dose on a mg/kg basis). All reactions were reversible, but the data suggest injection site reactions may be seen in the clinical setting. Haemocompatibility was demonstrated in an *in vitro* assay.

The proposed specifications for impurities in the drug substance and degradants in the drug product are either below the ICH qualification thresholds or have been qualified.

In summary, only limited toxicology data were submitted. Published data with vasopressin analogues provides sufficient evidence of human fetal risk, supporting the proposed Pregnancy Category (D). The repeat dose toxicity studies were of 28 days duration. The short daily exposure to terlipressin, particularly in the studies in rats, indicates toxicities

associated with prolonged vasoconstriction would not have been seen. Doses in the studies in dogs were generally quite low, and there were some discrepancies in the conduct of the pivotal study that impacts on the reliability of the findings.

The full toxicological profile of terlipressin acetate is unlikely to have been revealed in the submitted data and the nonclinical studies were considered inadequate for a satisfactory risk assessment, and hence do not offer adequate support for the registration of terlipressin acetate (Lucassin) for the proposed clinical use. It was recognised that terlipressin has been in clinical use for more than 20 years in Europe, and therefore there may be sufficient clinical experience to offset the deficiencies in the nonclinical submission.

The sponsor contended that the nonclinical data should not be interpreted in isolation in the assessment of the risk/safety profile of terlipressin, citing a number of figures relating to clinical usage and citing a number of publications regarding postmarketing experience in other countries. It was, however, noted that it is not the realm of the nonclinical evaluator to comment on the clinical data. The conclusions from the nonclinical data remain as stated above.

# IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings and the published references discussed can be found in Attachment 2.

### Introduction

The company submitted the following clinical information:

| Module 5 content relevant to this evaluation included |
|---|
| Population PK report |
| Literature study reports (PK/PD and efficacy ) |
| Study 0T-0401report (efficacy in patients) Data supplementing report |
| Study 0T-0401report (QT interval in patients) Data supplementing report |
| Study TAHRS report (efficacy & safety in patients) Data supplementing report |
| Literature reports |
| References |
| Addenda |

The revised search strategy for the literature was approved by the TGA.

The Addenda included addenda to the population PK study and to Study 0401that are considered under the relevant listings for the original studies and a 4 month New Drug Application (NDA) update that summarises the postmarketing data and literature published since the finalisation of the original sponsor Summary of Clinical Safety, they were reported as Addenda to the sponsor's Clinical Overview and Summaries of Clinical Efficacy and Safety. These were considered under safety and efficacy in this evaluation where relevant.

## Pharmacokinetics

A submitted population pharmacokinetic (PK) study was based on Study OT-0401 (since HRS Type 1 patients have severe hepatic and renal impairment). Supportive literature on PK in healthy volunteers was provided.

### Evaluator's overall conclusions on pharmacokinetics

While the statements in the first two paragraphs of the PK section of the PI are supported by the population PK study they are based on limited data and this is indicated in the PI.

Plate (1995)[18] stated that:

> *The half-life of terlipressin is reported to be approximately 24 minutes (Nilsson 1990, Forsling et al. 1980), the half-life of vasopressin is reported to be only six minutes.*
>
> *In our measurements, terlipressin and LVP were completely degraded after sixty minutes. Based on the assumption of a delayed terlipressin uptake in the organs, a maximum duration of action of two to three h can be extrapolated. This assumption corresponds well to the statements made by Forsling et al. in 1980 regarding a biological half-life of approximately 24 minutes and the findings by Kohaus regarding a clinical duration of action of two to three hours.*
>
> *Since a drug normally is excreted after five half-lives, a maximum duration of action of two h can also be extrapolated from the half-life. This would mean that in clinical applications terlipressin should be administered every two to three hours. The manufacturers' recommendations, however, are intervals of four to six hours.*

*Forsling 1980*[19] showed that the decay of terlipressin activity could be approximated to a double exponential. Taking the initial rapid decay phase, a mean half-life ($t_{1/2}$) for the disappearance of terlipressin was 24.2 ± 1.9 min (standard error (SE)).

*Nilsson 1990*[20] showed a $t_{1/2\alpha}$ of 8-9 min and a $t_{1/2\beta}$ of 51-66 min.

The PK modelling in healthy subjects gave a $t_{1/2\alpha}$ of 7 min and a $t_{1/2\beta}$ of 42min.

## Pharmacodynamics

Vasopressin is a potent vasoconstrictor. Pressor responses occur only with vasopressin concentrations significantly higher than those required for maximal antidiuresis; the vasopressin response reduces blood flow to nonessential organs, including the splanchnic bed, and increasing systemic blood flow with an increase in mean arterial pressure. In HRS patients and healthy volunteers receiving terlipressin the plasma level of lysine-vasopressin attained corresponds to the higher levels of vasopressin (>50 pg/mL) that activate $V_1$ receptors compared to the antidiuretic effect via $V_2$ receptors, which reach their maximum effect at lower concentrations (4-20 pg/mL). Additionally, a weaker agonist but in much higher concentrations, terlipressin has a vasopressin $V_1$ to $V_2$ receptor selectivity ratio of 2.2 compared to 1.0 for vasopressin.

The proposed PI contains under *Mechanism of Action* the statement that:

[18] Plate R. *Studies on the localization and kinetics in the degradation of the synthetic vasopressin slow-release preparation. Triglycyl-lysine-vasopressin. Analytical methods and pharmacological experiments*. Hanover, Germany: Hanover School of Medicine; 1995.
[19] Forsling ML, Aziz LA, Miller M, Davis R, Donovan B. Conversion of triglycylvasopressin to lysine-vasopressin in man. *J Endocr.* 1980; 85:237-244.
[20] Nilsson G, Lindbom P, Ohlin M, Berling R, Vernersson E. Pharmacokinetics of terlipressin after single IV. doses to healthy volunteers. *Drugs Exptl Clin Res.* 1990; 16:307-314.

*In HRS patients with hyperdynamic circulation, the V1 receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic area, results in an increase in effective arterial volume.*

The associated references[21, 22, 23] do not contain statements that terlipressin resulted in an increase in effective arterial volume.

The literature supports that terlipressin produces in HRS an increase in mean arterial pressure (MAP), while studies TAHRS & 0401 (p = 0.333) showed no effect and Study 0401 showed significant (p = 0.017) increase compared to placebo but this was minimal (2.36mmHg), most of the difference being due to a fall in the placebo group. The literature showed a non significant decrease in heart rate (HR) with terlipressin, as did Studies 0401[24] and TAHRS.[25]

While the literature showed that terlipressin produces in HRS normalisation of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system), the Studies TAHRS and 0401 showed no significant change.

The literature supports that terlipressin increases renal blood flow in cirrhotic patients with refractory ascites.

The literature shows that in cirrhotic patients terlipressin increases systemic vascular resistance and decreases cardiac output.

The report gives graphical evidence of the average difference in pre and post dose MAP, but these are not given in numerical form. The range of differences reported for the systolic and diastolic pressures is much greater than suggested in the proposed PI for MAP.

## Efficacy

### Evaluator's conclusions on clinical efficacy for the treatment of HRS Type 1

The introduction to Study report OT-0401 gives a median survival time in HRS Type 1 of 2-4 weeks. Also, patients with HRS who receive transplants have more complications and higher in-hospital mortality than those without HRS[26, 27, 28]). In addition HRS Type 1 patients may not survive long enough to receive a liver transplant.

Bataller quotes Rimola as a reference and makes the following comments:

*Immediately after transplantation a further impairment in renal function may be observed and more than one third of patients require haemodialysis (35% of patients with HRS as compared with 5% of cirrhotic patients without HRS).*

[21] Arroyo V, Jiménez W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. *J Hepatol* 2000; 32: 157-170.
[22] Kiszka-Kanowitz M, Henriksen JH, Hansen EF, Møller S, Bendtsen F. Effect of terlipressin on blood volume distribution in patients with cirrhosis. *Scand J Gastroenterol* 2004; 39: 486-492.
[23] Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal Syndrome. *Lancet* 2003; 362: 1819-1827.
[24] p = 0.055, Report section 7.4 page 332.
[25] P = 0.061, Table 4.3.49; Clinical study report
[26] Bataller R, Gines P, Arroyo V. Hepatorenal Syndrome. *Semin Liv Dis* 1997; 17:233-247.
[27] Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. *Gastroentology* 1987; 93: 148-156.
[28] Rimola found that Univariate analysis indicated that 7 of the 16 selected variables had prognostic significance for predicting mortality: the preoperative existence of renal impairment or of encephalopathy. The preoperative serum bilirubin (>16 mg/dl) and albumin levels. The postoperative occurrence of late renal impairment, liver graft failure and the occurrence of a serious postoperative infection. Analysing these variables only a serious postoperative infection (p < 0.001), livergraft failure (p < 0.001), and preoperative renal dysfunction (p < 0.01) were found to be independent indicators of a fatal outcome.

*Patients transplanted with HRS have more complications, spend more days in the ICU and in the hospital, and have a higher in-hospital mortality rate than patients transplanted without HRS. Despite this increased morbidity, long-term survival of patients transplanted with HRS is excellent, the probability of survival 3 years after transplantation being of 60%. This survival is only slightly reduced compared with that of patients transplanted without HRS (which ranges between 70% and 80%).*

Thus, based on this the maximum improvement possible in 3 year survival in patients with HRS would be 30%. Against this being possible Rimola found that there were 2 other independent variables apart from preoperative renal dysfunction that affected survival, and Bataller proposes a continuum of renal dysfunction in these patients.

*"suggests that in cirrhotic patients with ascites there is a continuum of changes in renal perfusion and HRS is the end of this spectrum."*

While it is assumed that HRS reversal improves outcome, Bataller makes no such claim:

*In this regard (poor prognosis), the use of therapeutic methods (TIPS, vasoconstrictor agents, dialysis) to improve renal function temporally and act as a "bridge" to liver transplantation may be of most benefit. Nevertheless, the efficacy of these methods should be evaluated in controlled investigations.*

The Study OT-0401 showed significant differences in HRS reversal and change in SCr with minimal overlap of CIs. The interpretation of the abandoned study TAHRS and the submitted literature do not refute these results but the numbers are small. Does this translate to a difference in outcome of HRS? This was the answer sought[29] by the TAHRS study which was terminated after 4 years (enrolled 46 patients) where the estimated sample size required to demonstrate a significant treatment difference was 431 patients/group. Neither study could show a significant difference in survival, though the Cochrane review (criticised above) did. Study 0401 also failed to show a difference in transplant free survival. Overall in Study 0401, terlipressin-treated patients received their transplants later (31 days) compared with the placebo-treated patients (21 days), however this depends more on the availability of transplant.

The mean SCr concentration in responders was 3.2 mg/dL in the terlipressin group and 3.0 mg/dL in the placebo group. The highest SCr of a responder patient was 5.6 mg/dL for terlipressin and 4.7mg/dL for placebo.

Excluding patients with baseline SCr ≥ 5.0 mg/dL, the incidence in the MTIT at Day 14 population of reversal of HRS in the terlipressin group was 17/33 (51.5%) while Treatment Success (sustained reversal HRS) was 13/33(39%) versus 7/34 (21%) in the placebo group for both parameters. Among those ten in the placebo group with SCr ≥ 5.0 mg/dL, none had treatment success or HRS reversal and there was 1/9 in the terlipressin group.

There was no difference in Dialysis rates in Study OT-0401 between the treatment groups and ICU/hospital stay was not reported, while in TAHRS there was no significant difference in hospital stay and dialysis rates were not reported.

A comparison of the terlipressin group responders versus non responders showed a significant difference between in survival in Study OT-0401. However, the baseline SCr affected HRS reversal (and survival), so was survival an effect arising from HRS reversal or was HRS reversal another screening test for likely survival?

[29] Primary objective: to investigate the effects of treatment with terlipressin and albumin on the survival of patients with hepatic cirrhosis and HRS Type 1 or 2.
To evaluate whether the improvement in renal function, in the event this occurs, results in an increase in the probability of survival to transplantation and in a reduction of post-transplant complications.

For the Terlipressin group the survival and transplant free survival was statistically greater to Day 90 in the Treatment Success and HRS reversal patients compared to the other terlipressin patients without these; but there were no differences in survival for HRS reversal or Treatment Success in the placebo group.

How did the placebo success or responders compare in survival with the terlipressin? The numbers were small but some similarity is seen in Overall Survival out to Day 30 and 90 for Treatment Success and for HRS reversal; while this holds true for Transplant Free Survival for Treatment Success patients, terlipressin HRS reversal patients were transplanted earlier (not statistically tested and only sourced for ITT).

**Table 3. Survival of Treatment Success patients Study OT-0401 ITT Population**

| | Terlipressin | | Placebo | |
|---|---|---|---|---|
| Day | Transplant Free Survival | Overall Survival | Transplant Free Survival | Overall Survival |
| 14 | 14(100%) | 14(100%) | 7(100%) | 7(100%) |
| 30 | 11(79%) | 12(86%) | 6(86%) | 6(86%) |
| 90 | 9(64%) | 10(71%) | 4(57%) | 4(57%) |
| 180 | 4(29%) | 5(36%) | 3(43%) | 4(57%) |

**Table 4. Survival of HRS reversal patients Study OT-0401 ITT Population**

| | Terlipressin | | Placebo | |
|---|---|---|---|---|
| Day | Transplant Free Survival | Overall Survival | Transplant Free Survival | Overall Survival |
| 14 | 19(100%) | 19(100%) | 7(100%) | 7(100%) |
| 30 | 12(63%) | 14(74%) | 6(86%) | 6(86%) |
| 90 | 10(53%) | 12(63%) | 4(57%) | 4(57%) |
| 180 | 5(26%) | 9(47%) | 3(43%) | 4(57%) |

**Table 5. Summary of Overall Survival up to Days 14, 30, 90 and 180 (Observed Cases ITT population)**

| Survived | Terlipressin n (%) | Placebo n (%) | P-value[a] |
|---|---|---|---|
| **Day 14** | | | |
| N | 56 | 56 | 0.930 |
| Yes[b] | 40 (71.4) | 39 (69.6) | |
| No | 16 (28.6) | 17 (30.4) | |
| Median Survival (days)[c] | NA | NA | |
| **Day 30** | | | |
| N | 56 | 56 | 0.447 |
| Yes[b] | 31 (55.4) | 35 (62.5) | |
| No | 25 (44.6) | 21 (37.5) | |
| Median Survival (days)[c] | NA | NA | |
| **Day 90** | | | |
| N | 56 | 56 | 0.811 |
| Yes[b] | 27 (48.2) | 24 (42.9) | |
| No | 29 (51.8) | 32 (57.1) | |
| Median Survival (days)[c] | 43.5 | 48.0 | |
| **Day 180** | | | |
| N | 56 | 56 | 0.839 |
| Yes[b] | 24 (42.9) | 21 (37.5) | |
| No | 32 (57.1) | 35 (62.5) | |
| Median Survival (days)[c] | 43.5 | 48.0 | |

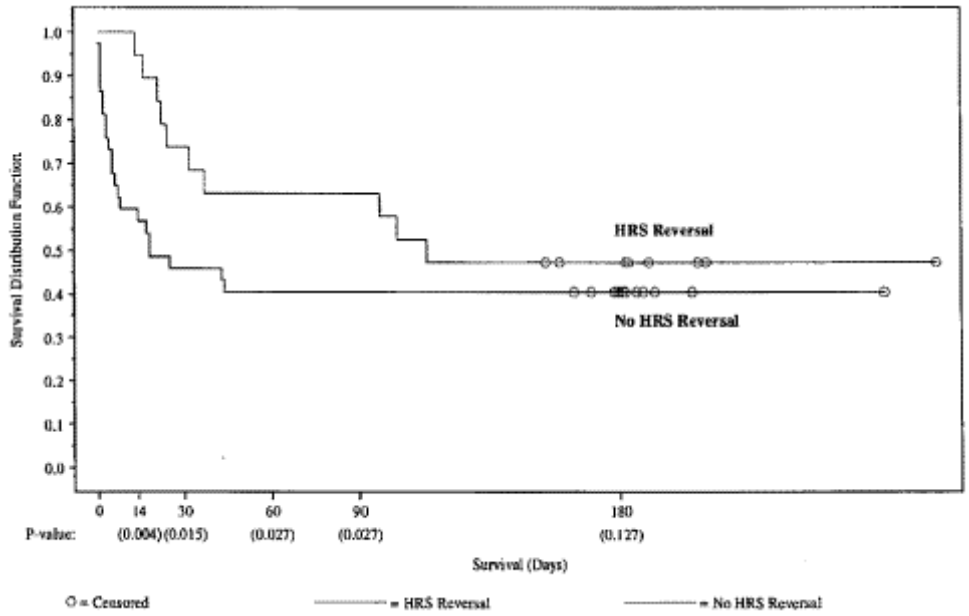
[a] From a two-sample log-rank test stratified by baseline strata (alcoholic hepatitis present or not). Includes data up to and including the time point. [b] Includes patients without a known death on or before the specified time point. [c]Calculated using product limit estimates. Cross Reference: Data Listings 10.1, 19, 24 and 25

**Table 6. Status of HRS Responders During Follow-up (ITT)**

| Status at Follow-up Time Point | Terlipressin (n=56) | Placebo (n=56) |
|---|---|---|
| **Total n with HRS Reversal** | 19 (34%) | 7 (13%) |
| | | |
| **Day 30 Status** | | |
| Alive | 14 (25%) | 6 (11%) |
| Transplant only | 2 (4%) | 0 |
| Dialysis only | 0 | 0 |
| Transplant + Dialysis | 0 | 0 |
| **Day 60 Status** | | |
| Alive | 12 (21%) | 4 (7%) |
| Transplant only | 2 (4%) | 0 |
| Dialysis only | 0 | 0 |
| Transplant + Dialysis | 0 | 0 |
| **Day 90 Status** | | |
| Alive | 12 (21%) | 4 (7%) |
| Transplant only | 2 (4%) | 0 |
| Dialysis only | 0 | 0 |
| Transplant + Dialysis | 0 | 0 |
| **Day 180 Status** | | |
| Alive | 9 (16%) | 4 (7%) |
| Transplant only | 4 (7%) | 0 |
| Dialysis only | 0 | 0 |
| Transplant + Dialysis | 0 | 1 (2%) |

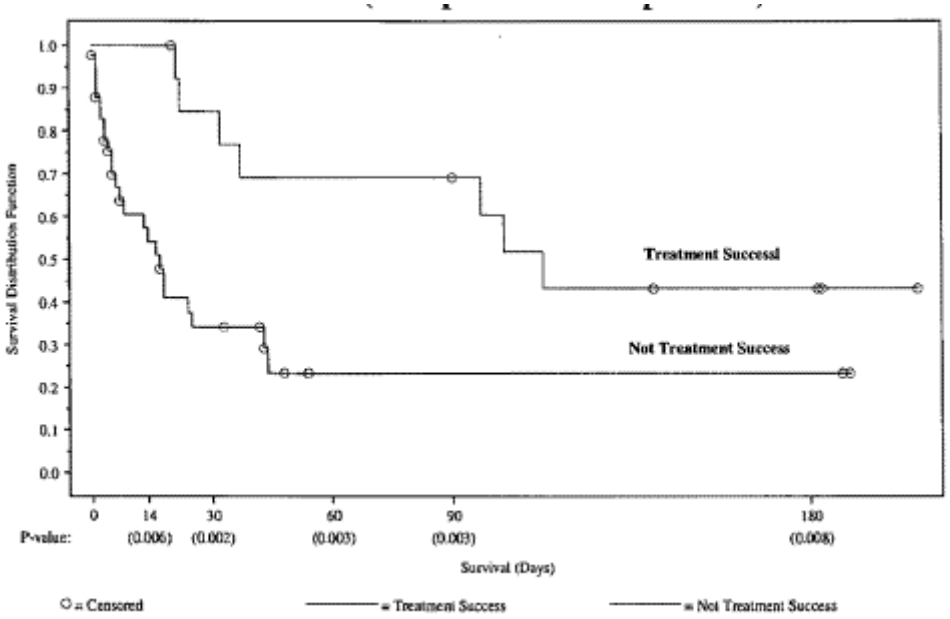
Number of patients with transplants is cumulative.

**Figure 2. Summary of Terlipressin Population Overall Survival for HRS Reversal versus No HRS Reversal (ITT)**



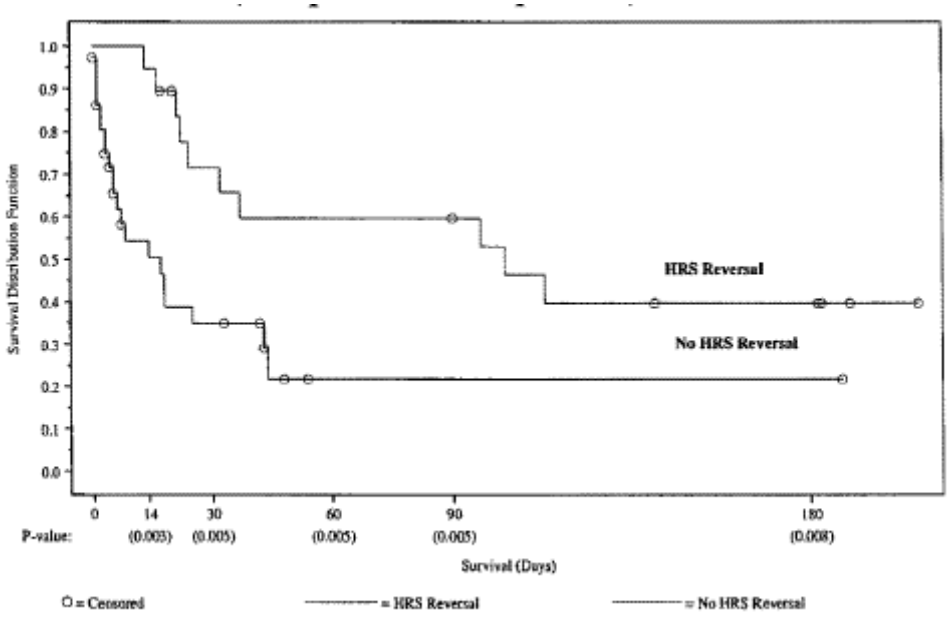

Note: From a two-sample log-rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

**Figure 3. Summary of Terlipressin Population Transplant-Free Survival for Treatment Success versus Not Treatment Success (ITT)**



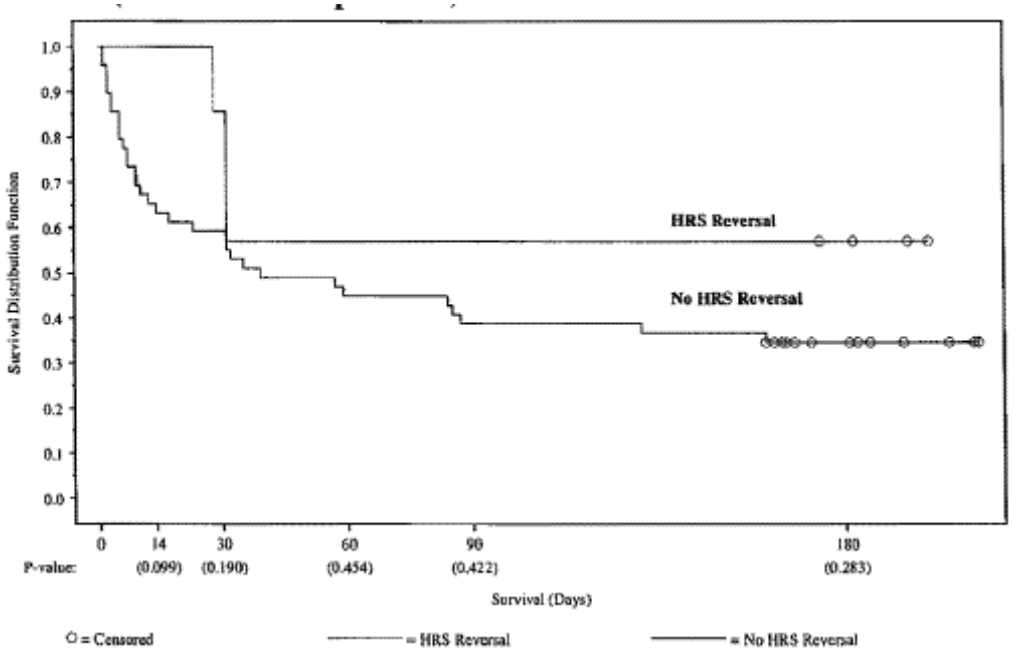

Note: From a two-sample log-rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

**Figure 4. Summary of Terlipressin Population Transplant-Free Survival for HRS Reversal versus No HRS Reversal (ITT)**



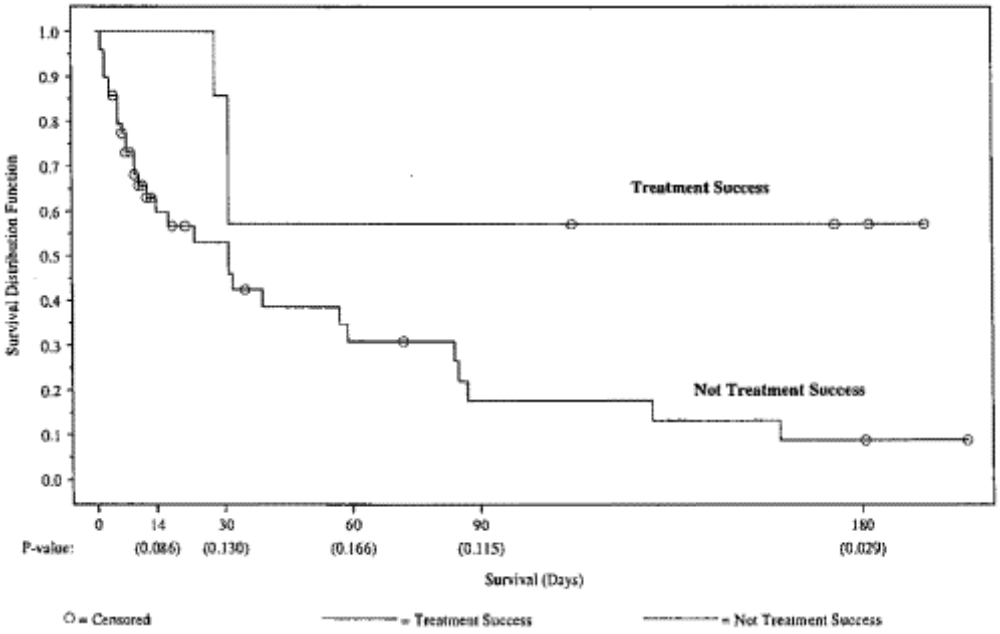

Note: From a two-sample loge rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

**Figure 5. Summary of placebo Population Overall Survival for HRS Reversal versus No HRS Reversal (ITT)**



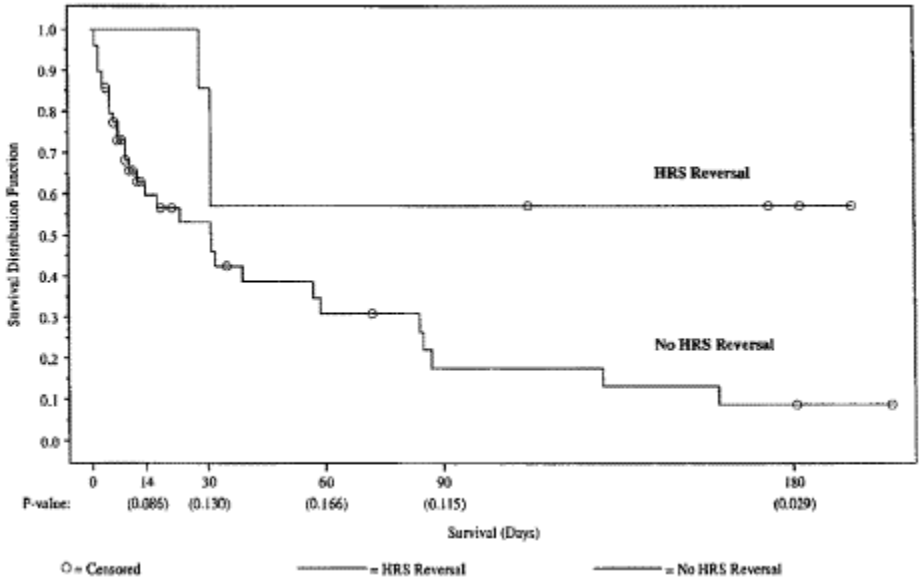

Note: From a two-sample log-rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

**Figure 6. Summary of Placebo Population Transplant-Free Survival for Treatment Success versus Not Treatment Success (ITT)**




Note: From a two-sample log-rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

**Figure 7. Summary of placebo Population Transplant-Free Survival for HRS Reversal versus No HRS Reversal (ITT)**




Note: From a two-sample log-rank test stratified by strata (alcoholic hepatitis present or not). Includes data up to and including the time point.

## Safety

Safety data from the OT-0401 and TAHRS studies were not pooled because OT-0401 had a double-blind design and TAHRS was an open-label study. In addition, there were some differences in dosing schedules (regimen and maximum allowable dose; *Pharmacokinetics* above) and patients in TAHRS who were randomised to the albumin arm were allowed to receive rescue (crossover) treatment with terlipressin.

The sponsor also made comparisons of safety results between the two despite the small numbers involved.

### Evaluator's overall conclusions on clinical safety

The patient numbers in the pivotal study for safety evaluation were small (56) these were subjected to intense review and comparison with those from TAHRS (23). Most of these patients had terlipressin for < 6 days.

The adverse event (AE) spectra across the databases, literature and trials are consistent and relate to the PDs of the drug:

- Gastrointestinal disorders; in particular abdominal pain/cramps
- Cardiovascular disorders; relating to vasoconstriction and including angina/infarction and skin ischaemia/necrosis
- Bronchospasm was a cause of death in the literature.

$Q_T$[30] prolongation was reported in the literature and who database. In the Study OT-0401 2/56 patients developed a $QT_cF$ interval > 500 ms.

The number of patients assessed for frequency of treatment–related AEs was 56 (Study OT-0401) where there was an incidence of 32% (18) that was compared to 23 patients (Study TAHRS) with an incidence of 78% (18). The sponsor offered possibilities, but was unable to explain the difference.

## List of questions

The evaluator made recommendations to the Delegate regarding the PI but these are beyond the scope of this AusPAR.

## Clinical summary and conclusions

### First round benefit-risk assessment

#### *Benefits*

There are two propositions supporting the benefit of HRS reversal:

1. *To prolong survival prior to liver transplant as patients wait on donor liver availability.*

Study 0401 failed to show a difference in transplant free survival. While for the Terlipressin group, transplant free survival was statistically greater to Day 180 in patients who had Treatment Success and HRS reversal compared to the other patients given terlipressin. For patients given placebo who had treatment success and reversal of HRS, differences in survival at Day 180 compared to other patients given placebo were also observed. Seven terlipressin-treated and 5 placebo-treated patients who had not received liver transplants were alive at Day 180. Thus the major clinical benefit of terlipressin would be from extending the duration of survival prior to transplant.

Demonstrating a survival benefit from treating the HRS-1 component amidst other concomitant life-threatening pathologies presents a challenging task. This was only

[30] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

partially met in the data submitted. It seems likely that for approximately 20% of patients terlipressin results in a few additional days to weeks of survival without a liver transplant. The clinical benefit of such a small increase in survival time depends on whether this additional time is likely to result in a clinically significant increase in the availability of a liver for transplant. Therefore the clinical benefit of terlipressin will vary with the availability of livers for transplant and it is thus not possible to estimate how many patients will receive transplants (and have increased probability of longer term survival) because of the use of terlipressin. Where few livers are available the benefit would be negligible.

2. *To achieve a more successful transplant as assessed by survival, hospital and ICU stay and dialysis rate.*

Neither study could show a significant difference in survival, although the Cochrane review did (unfortunately it included Yang 2001[31] who did not specify the HRS type of the patients and Pomier 2003[32] which related to the use of octreotide.)

Again in Study OT-0401for the terlipressin group the survival was statistically greater to Day 90 in the Treatment Success and HRS reversal patients compared to the other terlipressin patients without these; but there were no differences in survival for HRS reversal or Treatment Success in the placebo group.

There was no difference in Dialysis rates in Study OT-0401 between the treatment groups and ICU/hospital stay was not reported. In TAHRS, there was no significant difference in hospital stay while dialysis rates and ICU stay were not reported.

The Study OT-0401 showed significant differences in HRS reversal and change in SCr with minimal overlap of CIs. The interpretation of the abandoned Study TAHRS and the submitted literature do not refute these results but the numbers are small.

***Risks***

The survival of patients who were on terlipressin and did not have HRS reversal was comparable to patients on placebo who did not achieve HRS reversal. Overall there was no difference in survival between the terlipressin and placebo groups but those on terlipressin who achieved HRS reversal had better survival than those on terlipressin who did not.

The studies submitted had relatively small numbers exposed to terlipressin but showed considerable treatment related AEs; in Study OT-0401 where there was an incidence of 32% (18) that was compared to study TAHRS with an incidence of 78% (18).

More concerning was the incidence of treatment related deaths reported in the literature 7 among 1433 patients (0.5%) where the incidence of AEs was given.

Of particular concern was the incidence of cardiac and respiratory treatment related AEs in patients already with liver and renal dysfunction and the occurrence of skin and intestinal events (for example, necrosis) the increased the possibility of infection – given that infection affects survival in liver transplantation.[33]

[31] Yang YZ, Dan ZL, Liu NZ. Efficacy of terlipressin in treatment of liver cirrhosis with hepatorenal syndrome. *J Intern Med* 2001.
[32] Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome: A randomized, double-blind, placebo-controlled, crossover study. *Hepatology* 2003; 38: 238-243.
[33] Rimola 1987. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. *Gastroentology* 1987; 93: 148-156.

### *Benefit-risk balance*

The benefit-risk balance of terlipressin given the proposed usage was considered unfavourable.

### Recommendation regarding authorisation

It was not recommended that terlipressin be registered for the Indication proposed.

# V. Pharmacovigilance findings

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 7.

**Table 7. Summary of the Ongoing Safety Concerns as specified by the sponsor**

| | | |
|---|---|---|
| **Important identified risks** | Cardiovascular: | myocardial ischaemia |
| | Respiratory: | wheezing/bronchospasm, dyspnoea, pulmonary oedema |
| | Gastrointestinal: | vomiting, diarrhoea, abdominal pain, intestinal ischaemia |
| | Skin Disorders: | peripheral cyanosis, livedo reticularis |
| | Electrolyte disturbances: | hypomagnesaemia |
| **Important potential risks** | Cardiovascular: | Torsade de Pointes, QT prolongation and ventricular fibrillation |
| **Important missing information** | None identified | |

The OPR reviewer considered that the summary of the Ongoing Safety Concerns was acceptable.

### Pharmacovigilance plan

The sponsor proposed to undertake routine pharmacovigilance activities for all of the ongoing safety concerns.[34]

In addition, the sponsor has proposed to undertake enhanced pharmacovigilance through the provision of safety information and active encouragement to health professionals

[34] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

(physicians, nurses, hospital pharmacists) for the submission of spontaneous reports when adverse events are identified.

The OPR reviewer had no objection to the sponsor undertaking routine pharmacovigilance activities for all of the ongoing safety concerns. Furthermore, the proposal by the sponsor to actively encourage the submission of spontaneous reports when an AE is identified during the initial postmarketing period was supported by the OPR reviewer. Given terlipressin will only be used in hospitals where prescribing will routinely be by specific specialists, this is a very practical proposal and will assist in the early identification of any changes in the adverse event profile.

### Risk minimisation activities

As no additional risk minimisation activities were proposed, there is no risk minimisation plan.[35]

The sponsor has stated that post-authorisation, they will be providing relevant product literature to physicians, nurses, pharmacists who are involved with the management of HRS-1 patients within hospitals. These include:

- The approved Lucassin PI;
- Physician's guide to prescribing Lucassin; and
- Contact details of local safety officer for adverse events reporting.

Although the OPR reviewer had no objection to the sponsor only undertaking routine risk minimisation, the sponsor stated that they will provide a 'Physician's guide to prescribing Lucassin' to health professionals. As no additional information was provided it was not entirely clear whether this guide is intended as an educational tool/additional risk minimisation activity. It was recommended to the Delegate that the sponsor be required to provide a copy of the 'Physician's guide to prescribing Lucassin'; if a copy is not yet available, the sponsor should provide further details on the information that will be provided in the guide.

Furthermore, the sponsor should provide further information on the "local safety officer for adverse event reporting". It is not clear if this refers to a contact person within each hospital where terlipressin will be administered or if the sponsor is referring to an employee within their organisation. In addition the sponsor should indicate if they will provide the details for reporting adverse events directly to the TGA.

### Summary of recommendations

The OPR recommended that the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration.

It was recommended to the Delegate that the sponsor be required to provide a copy of the 'Physician's guide to prescribing Lucassin'; if a copy is not yet available, the sponsor should provide further details on the information that will be provided in the guide. In addition the sponsor should provide further information on the "local safety officer for adverse event reporting".

[35] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

# VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

There were no quality objections to registration. Lucassin was discussed at the 140th PSC meeting in August 2011. The PSC agreed that the drug product should be labelled as containing 0.85 mg terlipressin, although the potential confusion with clinicians used to the dose being referred to as 1 mg was recognised. The PSC also made recommendations for amendments to the PI that were agreed to by the sponsor.

## Nonclinical

The nonclinical evaluator considered the overall toxicological component of the submission inadequate for a satisfactory risk assessment and hence did not offer adequate support for the registration of terlipressin acetate for the proposed clinical use. The evaluator noted that terlipressin had been in clinical use in Europe for over 20 years and suggested there may be sufficient clinical experience to offset the deficiencies in the nonclinical component of the submission.

The maximum non-lethal doses administered were 20 mg/ kg IV in mice, < 2 mg/kg IV in rats and 0.5 mg/kg IV in dogs; > 7 times the proposed 2 mg clinical dose on a body surface area basis. Deaths were attributed to severe vasoconstriction, a pharmacological effect. Repeat dose toxicity studies to 28 days were conducted in rats and dogs. Effects were seen in the kidneys, lungs, and testes attributable to the pressor activity of terlipressin. The nonclinical evaluator noted that due to aspects of the repeat dose study design the full toxicological profile of terlipressin is unlikely to have been revealed.

Terlipressin was not genotoxic. No carcinogenicity studies were submitted. This was accepted due to the short duration of use proposed and the negative genotoxicity findings.

Treatment related reactions were seen at injection sites in rats and dogs. Trace to severe perivascular inflammation was seen at about 3 times the proposed clinical dose on a mg/ kg basis.

The data suggested injection site reactions may be seen in the clinical setting.

The proposed specifications for impurities in the drug substance and degradants in the drug product are either below the ICH qualification thresholds or have been qualified.

## Clinical

### Clinical evaluation

The clinical evaluator recommended that terlipressin not be registered because of an unfavourable risk benefit balance. Terlipressin did not improve survival to 90 days in patients with HRS in the pivotal clinical trial (see also *Clinical Summary and Conclusion* above for further discussion).

### Pharmacology

Literature references and limited clinical trial data, including a population pharmacokinetics study of patients with HRS were submitted. Terlipressin is a vasopressin analogue. It is a prodrug, being converted to lysine vasopressin in the

circulation after the N-triglycyl residue is cleaved by endothelial peptidases. This results in a 'slow release' of the vasoactive lysine-vasopressin[1].

Pharmacokinetic data for terlipressin in healthy subjects were obtained from 2 published papers. In these studies terminal $t_{½}$ was approximately 1 hour, clearance approximately 9 mL/kg/min and mean Vd between 0.6 and 0.9 L/kg. Terlipressin is metabolised to lysine-vasopressin via sequential cleavage of the 3 glycyl groups. Once formed lysine-vasopressin is rapidly eliminated via various peptidase-mediated routes.

A population PK analysis was performed using data from subjects with HRS Type 1 enrolled in Study OT-401. This model predicted clearance of 0.375 L/h/kg (6.25 mL/kg/min) and median terminal t½ of 1.01 hours, similar to the values for these parameters in healthy subjects.

Terlipressin is not metabolised in blood or plasma. After IV administration the glycyl residues are cleaved in a stepwise fashion by endogenous proteases releasing lysine-vasopressin (LVP), the active metabolite. LVP is rapidly eliminated via peptidase-mediated routes. The majority of terlipressin metabolism occurs in liver and kidney. A small amount of terlipressin is excreted unchanged in urine. Terlipressin did not induce cytochrome P450 isoenzymes in *in vitro* studies in human hepatocytes.

The effects of terlipressin on heart rate, blood pressure, systemic and hepatic hemodynamic effects, skin blood flow, cerebral blood flow, antidiuretic effect and effect on coagulation were assessed either in clinical trials or reported in published papers of clinical trials.

There were 2 efficacy studies: TAHRS and OT-0401. In TAHRS mean arterial pressure (MAP) did not change significantly from baseline to end of treatment. In OT-0401 systolic blood pressure increased to 4.2 mmHg (3.9%) and diastolic blood pressure by 2.9 mmHg (4.6%) at 2 hours post-dose and transient decreases in heart rate (3 beats/min [3.4%]) were observed in patients given terlipressin. Changes in mean arterial pressure from baseline to end of study are shown in the CER. In patients with reversal of HRS the increases in MAP were greater in those patients given terlipressin than in those given placebo. For patients who did not have reversal of HRS, those given terlipressin had a lesser reduction in MAP than those given placebo. The effect of terlipressin on MAP was in the region of 3-4 mmHg difference compared with placebo both patients with reversal of HRS and those without reversal. Literature studies reported mean reductions in heart rate ranging from 2-8% patients with HRS given terlipressin.

In patients with cirrhosis a single dose of terlipressin was associated with reductions in hepatic venous pressure gradient, hepatic blood flow, portal venous blood flow, splenic blood flow and perfusion pressure while renal blood flow and perfusion pressure increased. The extent of change for these parameters is summarised in the CER. Terlipressin was also reported to cause decreases in skin blood flow in healthy volunteers and increases in cerebral perfusion and intracranial pressure in patients with acute liver failure.

In published studies terlipressin generally decreased plasma rennin, aldosterone and noradrenaline and increased atrial natriuretic peptide in cirrhotic and HRS patients with hyperdynamic circulation. In study OT-0401 reductions of 16% in rennin and 19% in aldosterone from baseline to end of study were noted in patients given terlipressin and albumin but these changes were not statistically significant. No significant differences were seen in study TAHRS. The extent of change in these vasoactive hormones is shown in the CER.

One published study in healthy volunteers showed an antidiuretic effect of terlipressin 7.5 µg/kg commencing within 60 minutes of administration with a progressive increase in urine osmolality during the 5 hours of observation. In 2 small studies from 1979/80

terlipressin did not affect levels of plasminogen activator, factor VIII or factor VIII-related antigen.

Four published studies examined drug interactions with terlipressin. These studies are summarised in the CER. Octreotide, prazosin and nitroglycerin each in combination with terlipressin resulted in small additional improvements in the hepatic venous pressure gradient that were greater than those seen with terlipressin alone. Most of the changes were not statistically significant however these were small studies. Human Atrial Natriuretic Polypeptide (ANP) in combination with terlipressin did not result in additional improvements or a trend to improved hemodynamic function in patients with cirrhoses and ascites.

**Efficacy**

Dose finding was limited. The dose regimen selected for the pivotal study was determined after a review of doses used in published studies and on the advice of the Terlipressin Clinical Advisory Board. Data from the population PK analysis of Study OT-0401 showed no correlation between response to exposure to terlipressin, assessed as AUC and HRS reversal response.

Two studies provided information on safety and efficacy and additional information was available from published studies. Only 1 double blind, placebo controlled study of terlipressin in patients with HRS Type 1 has been conducted.

Note the dose of 1 mg terlipressin diacetate stated to have been given in the pivotal study was actually 0.85 mg of terlipressin free base. This dose is referred to as 1 mg for consistency.

Study OT-0401 was a randomised, double blind, placebo controlled study of IV terlipressin in patients with HRS Type 1. It was conducted between 2004 and 2006 at 35 sites in the USA Russia and Germany. The primary objective was to demonstrate that IV terlipressin is safe and effective in the treatment of patients with HRS Type 1. Secondary objectives were to demonstrate that terlipressin improves renal function and survival compared to placebo.

There were 2 initial primary endpoints:

- *Treatment success* required an initial reduction of serum creatinine (SCr) to ≤ 1.5 mg/dL followed by a confirmatory SCr measurement of ≤ 1.5 mg/dL 48 hours after the initial HRS reversal and an additional SCr < 2.5 mg/dL at Day 14, without intervening liver transplant or dialysis. Patients who did not have an SCr collected at these 3 time points were considered non-responders.
- *HRS reversal* defined as the number of patients who demonstrated reversal of HRS (SCr ≤ 1.5 mg/dL on at least 2 measurements obtained 48 ± 2 h apart), without intervening dialysis or liver transplantation divided by the total number of patients in the ITT population.

Following review of the study data, which did not show a statistically significant difference in treatment success between terlipressin and placebo and on discussion with the FDA, the primary endpoint was amended and additional SCr values collected from patients medical records were incorporated into a re-analysis of the data. The revised primary efficacy parameter was *treatment success at Day 14* defined as the percentage of patients who were alive at Day 14 and who demonstrated a reversal of HRS (SCr ≤1.5 mg/dL on ≥ 2 measurements obtained 48±8 h apart), without dialysis or recurrence of HRS. Other efficacy endpoints included measures of renal function and overall and transplant free survival up to Day 180.

Patients received either terlipressin starting at 1 mg every 6 h (q6h), increasing to 2 mg q6h after 3 days if the patient did not achieve a ≥ 30% decrease in SCr or placebo. Most patients also received albumin, this was initially titrated to a specific albumin level but was amended during the study such that all subsequent patients received a standard albumin dose (100 g on Day 1 and 25 g on each subsequent day until the end of study drug administration).

Patients were required to meet the International Ascites Club (IAC) diagnostic criteria for HRS Type 1 with some additions to allow for a homogeneous HRS Type 1 population. Patients with ongoing shock, uncontrolled bacterial infection, fluid loss, intrinsic or parenchymal renal disease or who were either receiving nephrotoxic drugs or who had liver disease as a result of drugs that were also nephrotoxic (for example, paracetamol overdose) were excluded from study.

For the initial definition of treatment success, where missing SCr values at Day 14 were imputed as "not a treatment success" both the ITT and MITT analyses failed to show a statistically significant difference between terlipressin and placebo. These results are shown in the CER. For the revised definition of treatment success at Day 14, in the ITT population a total of 16/56 (28.6%) of patients given terlipressin and 7/56 (12.5%) given placebo met the revised criteria for treatment success. This difference was statistically significant (p=0.037). Reversal of HRS was achieved in 19/56 (33.9%) patients given terlipressin and 7/56 (12.5%) patients given placebo (p = 0.008) for the ITT population. The difference for the MITT population was also statistically significant.

The CER shows the number of patients in each group alive at each time point through to 180 days. Follow up to Day 180 showed no significant differences in survival rates at any of the time points assessed (Days 14, 30, 60, 90 and 120). Twenty four patients given terlipressin and 21 given placebo remained alive at Day 180. Additionally transplant-free survival was similar in the 2 groups to Day 180. Overall, terlipressin treated patients received their transplants later (mean 31 days) compared with the placebo treated patients (mean 21 days). Thirteen patients who had responded to treatment (10 terlipressin and 3 placebo) had died as of the Day 180 follow up with none of these deaths attributed to relapse of HRS, the majority died as a result of their underlying liver failure.

Eighteen terlipressin and 17 placebo treated patients received a liver transplant up to Day 180 (6 given terlipressin and 5 given placebo in the ITT analysis). Seven terlipressin treated and 5 placebo-treated patients who had not received liver transplants were alive at Day 180.

Study TAHRS was a randomised, open, controlled study of terlipressin in patients with hepatic cirrhosis and HRS Type 1 or Type 2. The primary objective of this study was to investigate the effects of treatment with terlipressin and albumin on the survival of patients with hepatic cirrhosis and HRS Type 1 or 2. The study also planned to evaluate whether the improvement in renal function, if it occurred, resulted in an increase in the probability of survival to transplantation and in a reduction of post-transplant complications.

Patients had HRS Type 1 (73.9%) or 2 (26.1%) with SCr > 2.0 mg/dL. They were not required to be candidates for liver transplant. Patients were randomised to receive either terlipressin with 20% human albumin or 20% human albumin alone. Doses of terlipressin were from 3 to 12 mg daily given in divided doses every 4 hours with 20 to 40 g daily of albumin. This was a supportive study because it was open, included patients with HRS Type 2, did not use the terlipressin dose regimen proposed for registration, allowed crossover rescue therapy in patients not responding to albumin alone and was of limited size. It was terminated after 4 years with 46 patients enrolled. At that time the estimated sample size required to demonstrate a significant treatment difference in survival to

transplantation was 431 patients per group. To achieve this sample size would not have been possible within a reasonable time period so the study was terminated.

***Published studies***

Five randomised, placebo controlled studies, 5 non-randomised controlled studies, 1 case control study, 6 uncontrolled studies and 2 meta-analyses were presented to support efficacy and safety of terlipressin for the treatment of HRS Type 1. These studies/ analyses are summarised in the CER. A major difficulty in examining the literature was the inconsistency of the definition of responder and HRS reversal. These studies generally enrolled small numbers of patients with HRS Type 1 and reported small, not statistically significant differences in their efficacy endpoints between terlipressin and the comparator.

The Fabrizi meta-analysis published in 2006 initially considered data from 154 patients in 11 studies with 127 of these patients having HRS Type 1. This analysis was updated in 2009. These patients received from 1 to 6 mg/d terlipressin for from 2 – 26 days ± plasma expanders. Reversal of HRS was defined as a decrease in SCr to 1.5 mg/ dL or lower at the end of treatment with results presented for all patients (HRS Type 1 + HRS Type 2). A sub-analysis of 5 studies that included only patients with HRS Type 1 reported a pooled rate of HRS reversal of 0.53 (95%CI 0.41; 0.65). The update of this meta-analysis published in 2009, was not referred to in this submission.

The second meta-analysis, (Gluud 2006) included 3 randomised, controlled studies with a total of 51 patients. Two of the studies included only patients with HRS Type 1 and the third did not specify whether patients had Type 1 or Type 2 HRS. The terlipressin dose given was 1 mg bd and therapy duration varied from 2 to 15 days with maximum follow up to 14 days after treatment. Co-interventions included albumin 20 g/ day, fresh frozen plasma (150 mL qid), cimetidine (800 mg/d), sodium restriction, water restriction and dopamine infusion. 5/25 (20%) patients randomised to terlipressin and 15/23 (65%) randomised to the control group died. It was reported that terlipressin reduced mortality by 34% ((%%CI: -0.56 to -0.12).

There may have been some overlap in patients with the same patients included in more than one published study that was included in this meta-analysis. The clinical evaluator noted that control for bias in the Gluud meta-analysis was unclear.

**Safety**

Safety data from individual studies were not pooled due to design and enrolment differences between Studies OT-0401 and TAHRS. In these studies patients were exposed to terlipressin for a mean of 6.3 days with a maximum of 14 days in 0401 (n=56) and 7.8 days with a maximum of 32 days in TAHRS (n=23). In Study 0401 34 (60.7%) of patients given terlipressin withdrew compared with 45 (81.8%) given placebo.

The most frequent reasons for withdrawal were lack of efficacy (21.4% terlipressin versus 38.2% placebo); liver transplant (10.7% versus 9.1%) and death on treatment (10.7% terlipressin versus 5.5% placebo). In TAHRS the most frequent causes were lack of efficacy (4.3% for terlipressin versus 11% for placebo) and death on treatment (21.7% for terlipressin versus 13.0% for placebo).

In Study OT-0401 the incidence of adverse events and serious adverse events were similar in terlipressin and placebo groups but serious events and events considered treatment related were more frequent in the terlipressin group (treatment related AEs 32% versus 22% placebo; serious treatment related AEs 9% versus 2% placebo). In TAHRS adverse events were more frequently reported in patients given terlipressin (91% versus 71% placebo) as were events considered serious and/or treatment related. A much higher incidence of adverse events were considered treatment related in patients given in TAHRS

compared with 0401 (32.1% for terlipressin in 0401 versus 78.3% in TAHRS) and treatment related and serious (8.9% for terlipressin in 0401 versus 56.5% in TAHRS).

Differences in frequency of events with incidence of ≥ 10% grouped by System Organ Class are shown in the CER. In 0401 events from the SOCs *Respiratory, Thoracic and Mediasti*nal Disorders (39.3% versus 23.6% placebo) and Infections and Infestations (32.1% versus 20.0% placebo) were more frequent in patients given terlipressin than placebo. Individual adverse events reported more frequently in patients given terlipressin compared with placebo in 0401 were: anxiety (7% versus 2% placebo); hypomagnesaemia (7% versus 0% placebo); multi-organ failure (7% versus 0% placebo); sepsis (7% versus 2% placebo), wheezing, bradycardia, flatulence, pain extremities and pneumonia.

The above frequencies are quite different from those of TAHRS, suggesting the open nature of that study may have influenced adverse event reporting. In that study anxiety, hypomagnesaemia, and multiorgan failure were not reported at all and sepsis was reported in only 1 patient (given terlipressin) The largest differences were in the incidences of abdominal pain (21.7% versus 4.3% placebo) and diarrhoea (30.4% versus 8.7%). The most frequent events in patients given terlipressin were: diarrhoea, abdominal pain, acute pulmonary oedema, hepatic encephalopathy, intestinal ischemia, hepatic failure, HRS, dyspnoea and fluid overload.

Most ARs considered treatment-related were reported in only 1 patient. Adverse events leading to death at any time during study (to Day 180) are shown in the CER.

The most frequent causes of death associated with an adverse event in patients given terlipressin were: Hepatobiliary Disorders (29% terlipressin versus 38% placebo in 0401 and in 56% terlipressin versus 56% placebo in TAHRS); Infections and Infestations (10.7% terlipressin versus 1.8% placebo in 0401 and in 17.4% terlipressin versus 8.7% placebo in TAHRS). Deaths due to an adverse event in Renal and Urinary Disorders were reported in 4% terlipressin versus 7% placebo in 0401 and in no patients in TAHRS. Limited data from published studies concerned adverse events. Details of adverse events were generally sparse and information on deaths not consistently reported. The clinical evaluator noted that of 1433 patients reported on in published papers only 7 deaths were reported.

Uses other than HRS Type 1 were included in safety data from clinical trials. Overall the most frequently reported adverse events associated with terlipressin in published papers were: abdominal pain/cramps; pallor, increased bowel movements, hypertension and diarrhoea. Subsequent information from published papers also included pulmonary oedema as a more frequently reported adverse event. The WHO database included abdominal pain, chest pain substernal, vasospasm and headache as the most frequently reported adverse events associated with terlipressin.

The clinical evaluator considered the following events of regulatory importance: ischaemic, gastrointestinal, respiratory, cardiac events; infection and skin and subcutaneous tissues. In the clinical studies 1 patient given terlipressin in each of studies 0401 and TAHRS had myocardial infarction versus none in patients given placebo. No association between use of terlipressin and QT prolongation was apparent. In Study 0401 wheezing and bronchospasm were more frequent in patients given terlipressin (11% terlipressin versus none placebo) but was not reported in study TAHRS. In the clinical studies terlipressin was associated with a higher incidence of death due to infection but none of these deaths were attributed to use of terlipressin. There was no increase in reporting of skin and subcutaneous tissue vasoconstriction associated events in patients given terlipressin.

The clinical evaluator has noted that in the clinical trials, patients given terlipressin who did not have HRS reversal had lower survival rates than patients given placebo, though there was no statistical analysis of this and overall terlipressin made no statistically

significant difference to survival over any period up to Day 180 assessed in the pivotal clinical study.

### Sponsor response

The main contention of the sponsor's response to the clinical evaluation report was that the most appropriate efficacy endpoint should be a measure of the effectiveness in reversal of HRS, rather than survival. The clinical evaluation report has placed most emphasis on survival (at any of the time points measured). It was stated that large numbers of patients would be required to demonstrate a statistically significant effect on survival and that, as this is a rare condition, this was not practical. The HRS endpoints used in the pivotal study had been negotiated with another regulatory agency (the FDA), though terlipressin does not have a marketing authority for the proposed indication in the USA.

The sponsor also proposed that a small increase in survival time may allow for liver transplant or for recovery from an episode of decompensated cirrhosis caused by a reversible event.

The sponsor also noted the clinical evaluator's concern that the survival rate was lower in the non-responders given terlipressin than in patients given placebo (responders and non-responders). When the analysis was of non-responders only in each group the survival rates were comparable.

The sponsor produced a Kaplan-Meier plot showing overall survival for HRS reversal versus no HRS reversal in the pivotal study. This plot includes patients given terlipressin in both the HRS reversal and non-reversal groups. This plot shows that HRS reversal correlates with survival. This analysis groups those patients who received terlipressin and did not respond with reversal and those who received placebo and also did not have reversal of their HRS. Patients given placebo and had reversal were grouped with those who received terlipressin and also had reversal of HRS. This analysis is useful in showing the extent of correlation between reversal of an episode of HRS and short term survival. The difference between proportion of patients surviving (with and without reversal of HRS) is greatest at Day 14, where from the plot it appears that approximately 40% of patients without reversal and 5% of those with reversal have died.

## Risk management plan

No additional risk minimisation activities were proposed and there was no risk minimisation plan. The sponsor proposed routine pharmacovigilance with enhanced pharmacovigilance through the provision of safety information and active encouragement to health professionals for the submission of spontaneous reports when adverse events are identified. The sponsor noted that terlipressin will be given in a hospital setting and has a well established, predictable safety profile.

Should Lucassin be approved, the sponsor intends to provide healthcare professionals with a Physicians Guide to prescribing in addition to the PI and contact details of the local safety officer. The Physicians Guide had not been made available at the time of completion of the RMP evaluation. The RMP evaluator accepted the proposed level of risk management activity.

## Risk benefit analysis

### Delegate considerations

Six months after an episode of HRS-1 very few patients are likely to be alive without a liver transplant. Any survival benefit appears to be mostly during the first 14 days after commencement of treatment and occurs only in a minority of patients. In the pivotal study, 7 terlipressin treated patients and 5 placebo treated patients who had not received liver transplants were alive at Day 180. Thus the major clinical benefit of terlipressin would be to extend the duration of survival prior to transplant, however it does not appear to do this for very long or for the majority of patients.

For the total population given terlipressin there was a mean difference of 9.7 days (median difference 7.5 d) in time to liver transplant in the overall patient population who received transplants (18 given terlipressin and 17 given placebo). These times are likely to vary depending on the availability of livers for transplant for an individual patient and are therefore not necessarily reproducible. No statistical analysis was performed on these data.

While it is clear that terlipressin has an effect in reversing HRS-1, no effect on survival was demonstrated at any time point assessed during the study for the overall patient population.

HRS-1occurs in end stage liver disease. As noted in the sponsor's response to the clinical evaluation report, HRS-1 is often one of a series of multiple concurrent life threatening complications in end stage liver disease. Demonstrating a survival benefit from treating the HRS-1 component amidst other concomitant life-threatening pathologies presents a challenging task. This was only partially met in the data submitted.

In the response to the clinical evaluation report the sponsor has shown that reversal of HRS correlates with a short term improvement in rate of survival (up to 90 days) with the maximal difference in proportion of survivors at day 14 of treatment.

In the pivotal study terlipressin was shown to reverse HRS-1 in 19/56 (33.9%) patients given terlipressin versus 7/56 (12.5%) patients given placebo ($p = 0.008$) for the ITT population. The absolute difference in HRS reversal was approximately 20% and it is these patients who may have some short term survival benefit from treatment, with the difference in survival rates being most apparent at 14 days from commencement of treatment. For 80% of patients with HRS Type 1 there was no benefit from treatment with terlipressin.

It seems likely that for approximately 20% of patients terlipressin results in a few additional days to weeks of survival without a liver transplant. The clinical benefit of such a small increase in survival time depends on whether this additional time is likely to result in a clinically significant increase in the availability of a liver for transplant. Therefore the clinical benefit of terlipressin will vary with the availability of livers for transplant and it is thus not possible to estimate how many patients will receive transplants (and have increased probability of longer term survival) because of the use of terlipressin. Where few livers are available the benefit would be negligible.

The Delegate proposed to reject Lucassin (terlipressin) for treatment of hepatorenal syndrome (HRS) Type 1 because HRS-Type 1 occurs in the setting of end stage hepatic failure. Treatment of HRS-Type 1 does not affect the underlying hepatic failure. Although terlipressin is better than placebo in reversing HRS-1 it has not been shown to increase survival to a clinically significant extent in either the total population given terlipressin or in any subgroup of patients with HRS Type 1.

While a short term increase in transplant free survival probably occurs for those 20% of HRS-Type 1 patients who respond to treatment, the medium to longer term survival of

these patients will depend on the availability of livers for transplantation. The probability of a suitable liver becoming available during the additional days probably (but not statistically proven) to be gained from use of terlipressin would be variable but very likely to be extremely low in Australia at present.

While terlipressin may well improve renal function in patients with HRS before transplantation to avoid dialysis and significant renal impairment as stated by Professor McCaughan, this was not the proposed indication and evidence towards that use was not the subject of this submission.

The advice of the ACPM was particularly requested on:

- Whether survival is the appropriate endpoint for assessment of efficacy or whether, as proposed by the sponsor, some measure of reversal of HRS Type 1 is more appropriate.
- Given overall medium to longer term survival of a patient with HRS Type 1 is dependent on a liver transplant could Lucassin be registered with a limited indication permitting use in HRS Type 1 only when it is likely a liver will become available for transplant to that patient in the near future?
- If the latter is acceptable, what limitations could be placed in the indications to reflect this limited patient access? Given the lack of ability to predict the availability of suitable livers for transplant to any individual patient how could such a limited access system be managed?

**Response from sponsor**

The sponsor noted that the Delegate proposed to reject the application for Lucassin (terlipressin) in the treatment of hepatorenal syndrome (HRS) Type 1 (HRS-l), because *"it has not been shown to increase survival to a clinically significant extent".* Although the Delegate acknowledged that *"terlipressin is better than placebo in reversing HRS-1",* the ultimate tests applied for the determination of clinical significance were based on two factors other than HRS reversal: (i) extent of transplant free survival benefits, which the Delegate described as *"additional days"* and *"short term";* (ii) likelihood of liver availability during the extended survival period.

The Delegate further sought particular advice from the ACPM on: *"whether survival is the appropriate endpoint for assessment of efficacy or whether ... some measure of reversal of HRS Type 1 is more appropriate";* and, whether/how Lucassin could be registered with a limited indication permitting use only when it is *"likely a liver will become available for transplant to that patient in the near future."*

The sponsor disagreed with the Delegate's conclusions on the grounds that: (a) HRS reversal is *the* appropriate endpoint for HRS-l, which has been largely overlooked; (b) the Delegate's over-emphasis on the survival data is disproportionate to the fact that it is supportive evidence, and that definitive treatment differences for such measures cannot be practically characterised; (c) the premise of the assessment which includes liver availability, is flawed; (d) the conclusions reached are unreasonable and substantially under-represent the true efficacy of the product.

In terms of the indication, the sponsor maintained that approval of Lucassin for the original proposed indication is justified based on the evidence submitted and the following contentions:

*Lucassin is indicated for the treatment of patients with hepatorenal syndrome (HRS) Type 1.*

Accordingly, the indication statement in the proposed Product Information (PI) was not modified.

Should the TGA*I* ACPM consider it necessary to provide further guidance on the use of the product in order to grant approval the sponsor proposed the following alternative indication statement for consideration:

> *Lucassin is indicated for the treatment of patients with hepatorenal syndrome (HRS) Type 1.*
>
> *Consultation with a local transplant unit is recommended to discuss suitability of treatment and liver transplant referral/assessment.*

No further changes were proposed to the dosage and administration information.

The key elements of the sponsor's contentions are summarised below.

***HRS reversal versus survival***

- In the HRS-l setting, renal measures based around HRS reversal are the appropriate primary endpoints, not survival. The Delegate's deliberation reflects an over-emphasis on the *supportive* survival data, with insufficient weight given to the *primary* outcomes based around HRS reversal. This is unreasonable as it is inconsistent with the broad acceptance of HRS reversal as a clinically relevant endpoint in HRS-l and disregards the fact that survival treatment differences cannot be practically characterised.
- The accepted therapeutic goal of improving renal function in HRS-l, that is, HRS reversal, is unequivocal.
- The benefit and clinical relevance of the rapid correction of acute renal failure in the setting of liver disease is well supported by the literature, clinical guidelines and a recent statement from the Australian Liver Association ('ALA Statement').
- Furthermore, while survival outcomes cannot feasibly be investigated in HRS-l (see below), HRS reversal is a measurable endpoint that has been shown to correlate strongly with improved survival. For the liver transplant setting, the data suggests that HRS reversal can provide clinically significant additional survival time to allow organ procurement which can be life saving for the patient.
- The over-emphasis by the Delegate on the supportive survival data is unreasonable considering that the submitted studies were not intended nor were they powered to detect survival treatment differences; and that studies of such power are practically impossible to execute for the proposed orphan HRS-l indication.
- Given that survival outcomes cannot be robustly investigated in this indication, the sponsor contended that the primary HRS reversal data should rightly be the principal determinant of the drug's efficacy.

***The premise of the efficacy assessment is unreasonable; the conclusions reached underestimated treatment benefits***

- The Delegate's negative recommendation essentially means that patients with HRS-l should not be treated with terlipressin, and instead receive IV albumin alone. The consequence of this would be an increased likelihood of mortality within 30 days, or if the patient receives a liver transplant, emerge from the transplant with progressive renal disease, increased morbidity and mortality. Clearly, this is clinically undesirable.
- Liver availability features prominently in the Delegate's deliberation. However, the sponsor contended that the regulatory assessment of any drug should be based upon its intrinsic properties demonstrated in the target population, rather than on an unpredictable external factor (liver availability) over which no one has any control. Based on the Delegate's reasoning, it would be extremely difficult to have any drug approved for HRS-l where liver availability happens to be very low during a particular time period. Thus, the sponsor contended that liver availability is an unreasonable test

to apply for the determination of regulatory approval. For a critically ill patient presenting with HRS-1, good medical practice dictates that the best treatment be given to stabilise the patient, *irrespective of liver availability.*

- It is also problematic that, in determining that the clinical benefit of terlipressin is not of a "clinically significant extent", the Delegate has not quantitatively defined with justification, as to what would constitute a clinically significant benefit.
- The Delegate's interpretation of the efficacy data reflects an underestimation of the clinical benefits achieved with terlipressin.

***True extent of the clinical benefits with terlipressin***

- Of the pivotal study OT-0401, the Delegate commented that, "it is clear that terlipressin has an effect in reversing HRS-1 ... The absolute difference in HRS reversal was approximately 20% ". In essence, the data shows that patients treated with terlipressin were approximately three times more likely to achieve HRS reversal (primary endpoint) than compared to placebo (33.9% versus 12.5%).
- When responder analyses were undertaken, a strong correlation was shown to exist between the primary endpoint of HRS reversal (as well as Treatment Success) and survival. Of this, the Delegate described the survival gain variously as, ''few additional days to weeks of survival without a liver transplant" and “additional days".
- The sponsor argued that none of the stated durations accurately reflects the significantly higher rates of transplant free survival for HRS reversal compared to no HRS reversal observed to 180 days in both the terlipressin and placebo groups. The significance of this survival benefit in HRS reversal responders is reinforced by a recently plotted Kaplan-Meier plot, which pools the data across the two treatment groups. The key findings from this plot were that: (i) The differential in transplant-free survival for HRS reversal versus no HRS reversal, which reached 37% at Day 14, was sustained to Day 180 (40% differential); (ii) The survival gains in patients with HRS reversal were far in excess of "a few days" or "weeks"; (iii) half of the patients achieving HRS reversal were still alive at 180 days without a transplant, compared with a dismal 10% where no HRS reversal was achieved.
- The above takes on even greater significance when one considers the data in the ANZ Liver Transplant Registry (http://www.anzltr.org/statistics.html), which indicates that in 2010, the median time to transplant was 84 days.

***Benefit risk conclusion***

Patients presenting with HRS-l are critically ill and face real danger of imminent mortality. In clinical practice, the presentation of a very sick patient with acute renal failure associated with HRS-l are indicators for rapid assessment of suitability for liver transplantation and, if found suitable, then rapid elevation up the list for receiving donor organ. According to the data from the ANZ Liver Transplant Registry, the median time to transplant was 84 days in 2010.

In the setting of HRS-1 terlipressin has been shown to be efficacious in reversing the acute renal failure that is the central, life threatening feature of the condition (HRS reversal). By reversing HRS, the transplant-free survival of patients can be significantly extended by up to 180 days. These are highly clinically significant benefits which refute the Delegate's conclusion of *'few additional days to weeks of survival".* The clinical implications of these benefits are that:

(i) For HRS-1 patients awaiting donor organ who respond to terlipressin treatment, their chance of successful bridging to curative transplantation is greatly improved, considering a median time to transplant of 84 days.

(ii) For patients yet to have been assessed for transplant suitability, terlipressin allows time for this to be expedited, along with procurement of donor organ.

(iii) Where transplantation is not possible, reversal of HRS provides additional time to allow clinically significant recovery of the underlying decompensated liver disease, particularly in the setting of decompensated cirrhosis provoked by a reversible event, for example, alcoholic hepatitis.[36]

In terms of safety, this was not raised as an issue in the Delegate's closing remarks. As previously discussed in the sponsor's response to the CER, the adverse events (AEs) of terlipressin are predictable and recognisable and, since terlipressin is used within hospitals under a high vigilance setting, drug related AEs can be anticipated, recognised, and promptly managed.

Given these findings, the Delegate's negative recommendation on Lucassin is unreasonable which, if upheld, would be counterproductive and deleterious to patient care and their survival outcomes.

The efficacy/safety findings clearly weigh in favour of a positive benefit risk profile, further reinforced by the critical unmet need in an orphan HRS-l population that terlipressin would fulfil.

**Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

***Efficacy***

Overall, the small data set has demonstrated that this product has sufficient efficacy when the end point of HRS reversal is considered; however, the measurement of survival is the most appropriate clinical end point for hepatorenal syndrome Type 1. Few patients presenting with HRS 1 survive beyond 180 days without a liver transplant. It is noted that there are a range of external factors impacting on the timing for transplant organ availability and therefore the difficulty of using survival as an end point.

The evidence supports limiting the indication to include only the patient population who are actively being considered for a liver transplant.

The sponsor should be encouraged to conduct further studies on the likelihood and duration of survival and to include data points for patients who do not respond to this product.

***Safety***

Despite the significant side effect profile of this product it has a record of safe use that can be attributed to its restriction to use by experienced health professionals. This restriction must be continued.

***Indication***

The ACPM considered this product to have a positive benefit risk profile for the indication of:

> *Lucassin is indicated for the treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for a liver transplant.*

The ACPM also made a recommendation concerning the PI but this is beyond the scope of this AusPAR.

[36] Gonwa 1995: Impact of pretransplant renal function on survival after liver transplantation.

The ACPM advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Lucassin would support the safe and effective use of this product.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lucassin terlipressin 0.85 mg powder for Injection vial, indicated for:

> *The treatment of patients with hepatorenal syndrome (HRS) Type 1 who are actively being considered for a liver transplant.*

### Specific conditions applying to these therapeutic goods

The implementation in Australia of the terlipressin Risk management Plan (RMP) version 2, dated 27 July 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

# Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Attachment 2. Extract from the Clinical Evaluation Report

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