NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Terlipressin Acetate AFT 1 mg/8.5 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 8.5 mL contains 1 mg terlipressin acetate (equivalent to 0.85 mg terlipressin).

Excipient(s) with known effect:

One vial contains 1.33 mmol sodium.

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

3 PHARMCEUTICAL FORM

Solution for injection. Clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Terlipressin Acetate AFT is indicated in for the treatment of:

- Bleeding Oesophageal Varices (BOV)
- Type 1 Hepatorenal Syndrome, characterised by spontaneous acute renal insufficiency, in patients suffering from severe cirrhosis, with ascites.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dose and method of administration differs depending on the indication.

Bleeding Oesophageal Varices (BOV)

Intravenous injection (bolus): 2 mg terlipressin acetate every 4 hours by bolus injection. The treatment should continue until bleeding has been controlled for 24 consecutive hours or for a maximum period of 48 hours. After the initial injection, subsequent doses can be reduced to 1 mg terlipressin acetate every 4 hours in patients with a body weight of less than 50 kg or when necessitated by adverse effects.

Type 1 Hepatorenal Syndrome (type 1 HRS)

Intravenous injection (bolus): Terlipressin Acetate AFT is usually started at a dose of 1 mg of terlipressin acetate every 4-6 hours.

If serum creatinine does not decrease by at least 25% after 2 days, the dose can be increased in a stepwise manner up to a maximum of 2 mg terlipressin acetate every 4 hours.

Intravenous infusion (continuous): As an alternative to bolus injection, terlipressin can be administered as a continuous intravenous (IV) infusion with a starting dose of 2 mg of terlipressin acetate/24 hours and increased to a maximum of 12 mg of terlipressin acetate/24 hours. Administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see section 5.1).

Terlipressin Acetate AFT treatment is to be pursued until serum creatinine levels has decreased to < 133 µmol/litre (1.5 mg/dL). For patients with partial response (i.e. serum creatinine levels does not decrease to < 133 µmol/l), or patients without response (i.e. no reduction of serum creatinine levels), treatment should be discontinued within 14 days.

There is some data suggesting that terlipressin treatment may be more effective in patients with type 1 hepatorenal syndrome when it is given with human albumin, compared to treating with terlipressin alone.

The dosing of human albumin should be in accordance with current guidelines. Close monitoring for signs or respiratory failure or fluid overload is recommended (see section 4.4).

Method of Administration

Terlipressin Acetate AFT must only be administered intravenously (IV) by bolus injection (BOV and type 1 HRS) or continuous infusion (type 1 HRS only).

Special populations

Renal impairment

Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442 µmol/L (5.0 mg/dL), unless the benefit is judged to outweigh the risks (see section 4.4).

Hepatic impairment

Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and/or a Model for End-stage Liver Disease (MELD) score ≥ 39, unless the benefit is judged to outweigh the risks (see section 4.4).

4.3 CONTRAINDICATIONS

- Pregnancy
- Hypersensitivity to terlipressin or any other excipients of the product listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Monitoring during treatment

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

Patients with cardiovascular and pulmonary disease

Particular care is required in management of patients with cardiovascular or pulmonary disease since terlipressin may induce ischaemia and pulmonary vascular congestion (see section 4.8).

Caution should be exercised in treating patients with hypertension. In these patients, treatment should only be initiated after a careful clinical assessment of the potential risks and benefits.

Renal impairment

Prior to treatment of type 1 hepatorenal syndrome, other types of acute kidney injury should be ruled out. Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine > 442 µmol/L (5.0 mg/dL), when treated with terlipressin for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of adverse events, and increased mortality in this patient group have been observed in clinical trials (see section 4.2)

Hepatic impairment

Terlipressin should be avoided in patients with severe liver disease defined as Acute-on-Chronic Liver Failure (ACLF) grade 3 and / or a Model for End-stage Liver Disease (MELD) score ≥ 39, when treated with terlipressin for type 1 hepatorenal syndrome, unless the benefit is judged to outweigh the risks. Reduced efficacy in reversal of hepatorenal syndrome, increased risk of respiratory failure, and increased mortality in this patient group have been observed in clinical trials (see section 4.2).

Respiratory events

Fatal cases of respiratory failure, including respiratory failure due to fluid overload, have been reported in patients treated with terlipressin for type 1 hepatorenal syndrome.

Patients with a new onset of breathing difficulties or worsening of respiratory disease should be stabilized prior to receiving their first dose of terlipressin.

Higher doses of albumin may be associated with a higher risk of fluid overload and respiratory failure.

Caution should be exercised when terlipressin is administered together with human albumin as part of the standard care for type 1 hepatorenal syndrome. In case of signs or symptoms of respiratory failure or fluid overload, dose reduction of human albumin should be considered. If respiratory symptoms are severe or do not resolve, treatment with terlipressin should be discontinued.

Sepsis/septic shock

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

Terlipressin should be avoided in patients with septic shock with a low cardiac output unless the benefit is judged to outweigh the risks. Treatment with terlipressin may result in further reduction in cardiac output.

Injection site reaction

To avoid local necrosis at the injection site, the injection must be given intravenously.

Skin necrosis (unrelated to the injection site)

During post-marketing experience with terlipressin several cases of cutaneous ischaemia and necrosis unrelated to the injection site have been reported (see section 4.8). Patients with diabetes mellitus and obesity seem to have a greater tendency to this reaction. Therefore, caution should be exercised when administering terlipressin in these patients.

Torsade de pointes

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including “Torsade de pointes” have been reported (see section 4.8). In most cases, patients had predisposing factors such as basal prolongation of the QT interval, electrolyte abnormalities (hypokalemia, hypomagnesemia) or medications with concomitant effect on QT prolongation. Therefore, extreme caution should be exercised in the use of terlipressin in patients with a history of QT interval prolongation, electrolyte abnormalities, or concomitant medications that can prolong the QT interval (see section 4.5).

Children and the elderly

Particular caution should be exercised in the treatment of children and elderly patients, as experience is limited in these groups.

Excipients

This product contains 1.33 mmol of sodium per vial. This should be taken into consideration in patients on a controlled sodium diet.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The hypotensive effect of non-selective beta-blockers on the portal vein is increased with terlipressin. Concomitant treatment with medicinal products with a known bradycardic effect (e.g. propofol, sufentanil) may lower the heart rate and cardiac output. These effects are due to reflexogenic inhibition of cardiac activity via the vagus nerve due to the elevated blood pressure.

Terlipressin can trigger "torsade de pointes" (see sections 4.4 and 4.8). Therefore, extreme caution should be exercised in the use of terlipressin in patients with concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that may cause hypokalaemia or hypomagnesemia (e.g. some diuretics).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Treatment with terlipressin during pregnancy is contraindicated. Terlipressin has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. Terlipressin may have harmful effects on pregnancy and on the foetus.

Spontaneous abortion and malformation have been shown in rabbits after treatment with terlipressin.

Breast-feeding

It is not known whether terlipressin is excreted in human milk. The excretion of terlipressin in milk has not been studied in animals. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with terlipressin should be made taking into account the benefit of breast-feeding to the child and the benefit of terlipressin therapy to the woman.

Fertility

No human data on the effects of terlipressin on fertility is available. Animal studies do not indicate harmful effects of terlipressin on male fertility (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 UNDESIRABLE EFFECTS

Summary of safety profile

The most frequently reported undesirable effects in clinical trials are, abdominal pain, nausea, diarrhoea, pallor, dyspnoea (for type 1 HRS), respiratory failure (for type 1 HRS), vomiting and bradycardia.

The antidiuretic effect of Terlipressin Acetate AFT may cause hyponatraemia unless fluid balance is controlled. There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications (these are marked with footnotes).

Tabulated summary of adverse reactions

System Organ Class Disorder	VERY COMMON (>1/10)	COMMON (≥1/100 to <1/10)	UNCOMMON (≥1/1,000 to <1/100)	RARE (≥1/10,000 to <1/1,000)	FREQUENCY NOT KNOWN[a]
Infections and infestations		Sepsis/ septic shock [b c]			
Metabolism		Hyponatraemia			
Nervous system		Headache			
Cardiac		Bradycardia Chest pain Tachycardia	Atrial fibrillation Ventricular extracystoles [d] Myocardial infarction Torsade de pointes Cardiac failure		
Vascular		Vasoconstriction Peripheral ischaemia Pallor Hypertension Cyanosis	Hot flushes		
Respiratory, thoracic and mediastinal disorders	Dyspnoea [b] Respiratory failure [b]	Pulmonary oedema Respiratory distress [b] Dyspnoea [e]	Respiratory failure [e] Respiratory distress [e]		
Gastrointestinal	Abdominal pain	Diarrhoea Nausea Vomiting	Intestinal ischaemia		
Skin and subcutaneous			Skin necrosis (unrelated to the site of administration) [c d]		
Pregnancy, puerperium and perinatal conditions					Uterine hypertonus
Reproductive system and breast disorders					Uterine ischaemia
General disorders and administration site disorders			Injection site necrosis		

[a] Frequencies of these adverse events cannot be estimated from the available data

[b] Applicable to Type 1 HRS. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials

[c] See section 4.4 for further information

[d] Adverse reactions identified from post-marketing sources are presented by frequency category based on a theoretically calculated frequency if not observed in clinical trials.

[e] Applicable to Bleeding Oesophageal Varices

Description of selected adverse reactions

Safety related to method of administration

Based on results from a dedicated randomised multicentre trial in which the study population was patients with type 1 hepatorenal syndrome, administration of terlipressin as continuous IV infusion may be associated with lower rates of severe adverse events than with administration by IV bolus (see section 4.2 and 5.1).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportsnz/s/.

4.9 OVERDOSE

The recommended dose in the specific patient population should not be exceeded as the risk of severe circulatory adverse effects is dose-dependent.

Elevated blood pressure in patients with recognised hypertension can be controlled with 150 mcg clonidine intravenous. Bradycardia requiring treatment should be treated with atropine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues)

ATC code: H01B A04

Terlipressin (Triglycyl-Lysine-Vasopressin) is a synthetic analogue of the natural posterior pituary hormone vasopressin.

Terlipressin is a pro-drug with partial, intrinsic activity by itself. Terlipressin is transformed into the fully active metabolite lysine-vasopressin (LVP) by enzymatic cleavage. LVP remains within the therapeutic concentration range over a period of 4-6 hours. Doses of 1 and 2 mg terlipressin acetate effectively reduce the portal venous pressure and produce marked vasoconstriction. The lowering of portal pressure and azygos blood flow is dependent on dose. The effect of the low dose is reduced after 3 hours, while haemodynamic data show that 2 mg is more effective than 1 mg with a sustained effect throughout the treatment period of 4 to 6 hours.

Type 1 hepatorenal syndrome

The pathophysiology of type 1 hepatorenal syndrome is caused by the haemodynamic changes induced by portal hypertension seen in advanced cirrhosis. Terlipressin and its metabolites exert their effects via the vasopressin-1a receptor in vascular smooth muscle to induce splanchnic arterial vasoconstriction which results in a decrease of the portal pressure. Consequently, an improvement of the systemic circulatory function and redistribution of the effective arterial blood volume is observed. Lowering of portal pressure together with the improved systemic circulation leads to the suppression of the activity of the renin-angiotensin system and sympathetic nervous system, which are major triggers of excessive renal vasoconstriction, causing type 1 hepatorenal syndrome.

Clinical efficacy and safety

Continuous IV infusion versus IV boluses in the treatment of type 1 hepatorenal syndrome in patients with cirrhosis.

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

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics follows a two-compartment model with a rapid distribution phase.

Absorption

Terlipressin is administered by the intravenous route resulting in instant systemic exposure, requiring no absorption.

Distribution

In patients with liver cirrhosis with or without hepatorenal syndrome the distribution volume is in the range between 0.2 and 0.5 l/kg.

Biotransformation

The concentration of the active metabolite, lysine-vasopressin, starts to increase approximately 30 minutes after bolus administration of terlipressin and peak levels are reached between 60 and 120 minutes after administration of terlipressin.

Elimination

The elimination half-life of terlipressin is approximately 40 minutes in patients with liver cirrhosis with and without hepatorenal syndrome and the reported clearance is in the range between 5 and 9 ml/kg/min.

Linearity

Terlipressin demonstrated a dose-dependent and approximate proportional increase in total exposure (AUC) after single i.v. injections to healthy subjects (n=2-14 subjects per dose group) in a dose range between 5 and 30 µg/kg.

5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of single-and-repeat-dose-toxicity, and genotoxicity. At dosages relevant to humans, the only effects observed in animals were those attributable to the pharmacological activity of terlipressin. No pharmacokinetic data are available from animals but as the route of administration was intravenous, systemic exposure at multiples of the maximum human dosages can be assumed for the animal studies.

An embryo-foetal study in rats demonstrated no adverse effects of terlipressin, but in rabbits abortions occurred, probably related to maternal toxicity, and there were ossification anomalies in a small number of foetuses and a single isolated case of cleft palate.

In a rat fertility study, mating of terlipressin-treated males with untreated females had no effect on the number of matings and frequency of insemination but led to decreased post-natal litter size. Testicular atrophy and disturbances of

spermiogenesis observed in male rats treated with terlipressin for 3 weeks could not be confirmed. Likewise no testicular effects were seen in any other repeat-dose toxicity study in rats and dogs.

No carcinogenicity studies have been performed with terlipressin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium acetate

Acetic acid

Water for injection

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8 °C).

6.5 NATURE AND CONTENTS OF CONTAINER

Terlipressin Acetate AFT solution for injection is packed in a 10 mL clear glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused drug or waste materials should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.
Auckland
Phone: 0800 423 823
Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

3 April 2025

10 DATE OF REVISION

4 April 2025

Summary table of changes

Section changed	Details of change
6.3	Shelf-life changed to 36 months