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pharmaniaga®

Erylize

Terlipressin Acetate 1mg/8.5ml
Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT
Erylize 1mg/8.5ml 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.
Each ml contains 0.12 mg terlipressin acetate, corresponding to 0.1 mg terlipressin.
Excipient(s) with known effect: Sodium.
Each vial contains 1.33 mmol (30.5 mg) sodium. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear and colourless solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Treatment of bleeding oesophageal varices.
Treatment of type 1 hepatorenal syndrome, characterised by spontaneous acute renal insufficiency, in patients suffering from severe cirrhosis with ascites.

4.2 Posology and method of administration
Bleeding oesophageal varices
Adults: Initially an IV injection of 2 mg terlipressin acetate is given every 4 hours. The treatment should be maintained until bleeding has been controlled for 24 hours, but up to a maximum of 48 hours. After the initial dose, the dose can be adjusted to 1 mg IV every 4 hours in patients with body weight < 50 kg or if adverse effects occur.

Type 1 hepatorenal syndrome
Adults: Erylize is usually started at a dose of 1 mg of terlipressin acetate every 4-6 hours. The dose can be increased to a maximum of 12 mg daily, or 2 mg every 4-6 hours, if serum creatinine levels has not decreased by at least 25% after 3 days of treatment.

Treatment is maintained until serum creatinine levels has decreased to <133 µ mol/L (<1.5 mg/dL). For patients with partial response (i.e. serum creatinine levels does not decrease to <133 µmol/L), or for patients without response (i.e. no reduction of serum creatinine levels), treatment should be discontinued within 14 days.

Recurrent type 1 hepatorenal syndrome in responders, after the end of treatment is reported in up to 20% of cases. Retreatment with terlipressin is generally effective.

Data indicates that adding human albumin may be more efficacious than treating with terlipressin alone in patients with type 1 hepatorenal syndrome. The dosing of human albumin should be in accordance with current guidelines.

As an alternative to bolus injection, terlipressin can be administered as a continuous intravenous (IV) infusion with a starting dose of 2mg of terlipressin acetate/24 hours and increased to a maximum of 12 mg of terlipressin acetate/24 hours. If volume expansion is needed, Erylize can be diluted before administration (see section Other handling information). Administration of terlipressin as continuous IV infusion has been associated with lower rates of severe events than with administration by IV bolus (see section Pharmacodynamic properties).

Special populations
Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/L (5.0 mg/dL), unless the benefit is judged to outweigh the risks (see section Special warnings and precautions for use).

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 Special warnings and precautions for use).

Elderly:
There is no data available regarding dosage recommendation in the elderly.

Paediatric population:
There is no data available regarding dosage recommendation in the paediatric population.

METHOD OF ADMINISTRATION
Bleeding oesophageal varices: IV injection.
Type 1 hepatorenal syndrome: IV injection or IV infusion.

4.3 Contraindications
Contraindicated in pregnancy.
Hypersensitivity to terlipressin acetate or any of the excipients.

4.4 Special warnings and precautions for use
Warnings and precautions applicable to type 1 hepatorenal syndrome
Prior to treatment of type 1 hepatorenal syndrome, other types of acute kidney injury should be ruled out.

Renal impairment
Terlipressin should be avoided in patients with advanced renal dysfunction, i.e., baseline serum creatinine ≥ 442µmol/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 Posology and method of administration).

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 Posology and method of administration).

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 stabilised prior to receiving their first dose of terlipressin.
Caution should be exercised when terlipressin is administered together with human albumin as part of the standard of care for type 1 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.

Warnings and precautions applicable to all indications
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.

Patient with cardiovascular and pulmonary disease
Particular care is required in management of patients with cardiovascular or pulmonary disease since terlipressin may induce ischaemia and pulmonary vascular congestion. Caution should also be exercised in treating patients with hypertension.

Patients with septic shock
In patients with septic shock with a low cardiac output terlipressin should not be used.

Injection site reaction
To avoid local necrosis at the injection site, the injection must be given IV.

Skin necrosis
During post-marketing experience with terlipressin several cases of cutaneous ischaemia and necrosis unrelated to the injection site have been reported (see section Undesirable effects). 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 published clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including "Torsade de pointes" have been reported (see section Undesirable effects). 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 Interaction with other medicinal products and other forms of interaction).

Respiratory Effects
Terlipressin may cause smooth muscle constriction and should be used with caution and under strict monitoring in patients with severe asthma or chronic obstructive pulmonary disease (COPD).

Laboratory Monitoring
During treatment with terlipressin, serum creatinine should be monitored at least daily as terlipressin should be used with caution in patients with renal insufficiency. Fluid balance and electrolytes should be monitored carefully as hyponatraemia, hypokalaemia, hypomagnesaemia and other electrolyte disturbances have been reported.

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 medicinal product contains 30.5mg of sodium per vial, equivalent to 1.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products 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 or cardiac activity via the vagus nerve due to the elevated blood pressure.

Terlipressin can trigger "torsade de pointes" (see section Special warnings and precautions for use and Undesirable effects). Therefore, extreme caution should be exercised in the use of terlipressin in patients with concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidespressants 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 (see section Contraindications).
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 foetus.
Spontaneous abortion and malformation have been shown in rabbits after treatment with terlipressin.

Breastfeeding
It is not known whether terlipressin is excreted in human breast 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 breastfeeding 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.

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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
The most-frequently reported undesirable effects in published 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 may cause hyponatraemia unless the fluid balance is controlled. There are adverse reactions that appear twice in the table, as the estimated frequencies differ between indications.

Tabulated summary of adverse reactions

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1000 to < 1/100)	Frequency not known[a]
Infections and infestations		Sepsis/septic shock [b,c]		
Metabolism and nutrition disorders		Hyponatraemia		
Nervous system disorders		Headache		
Cardiac disorders		Chest pain Bradycardia Tachycardia	Atrial Fibrillation Ventricular Extrasystoles[d] Myocardial Infarction Torsade de pointes Cardiac failure	
Vascular disorders		Vasoconstriction Peripheral ischemia Pallor Hypertension Cyanosis	Hot flush	
Respiratory, thoracic and mediastinal disorders	Respiratory failure [b] Dyspnoea [b]	Pulmonary oedema Respiratory distress [b] Dyspnoea [e]	Respiratory distress [e] Respiratory failure [e]	
Gastrointestinal disorders	Abdominal pain	Diarrhoea Nausea Vomiting	Intestinal ischaemia	
Skin and subcutaneous tissue disorders			Skin necrosis (unrelated to the site of administration) [c,d]	
Pregnancy, puerperium and perinatal conditions				Uterine hypertonus
Reproductive system and breast disorders				Uterine ischemia
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 hepatorenal syndrome. Frequencies are calculated based on the pooled safety population in the OT-0401, REVERSE and CONFIRM clinical trials
[c] See section Special warnings and precautions for use for further information.
[d] Adverse reactions identified from post-marketing sources are presented by frequency category based on a theoretically calculated frequency if not observed in clinical trials.
[e] Applicable to Bleeding Oesophageal Varices

Description of selected adverse reactions

Safety related to method of administration
Based on results from a dedicated randomised controlled multicentre trial, administration of terlipressin as continuous IV may be associated with lower rates of severe adverse events than with administration by IV bolus (see section Posology and method of administration and Pharmacodynamic properties).

Post-marketing Experience
The following additional adverse reactions have been reported in post-marketing use: Ventricular fibrillation (frequency not known).

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

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

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 pituitary 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. 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.

Bleeding oesophageal varices
The pathophysiology of bleeding oesophageal varices is caused by the haemodynamic changes induced by portal hypertension leading to redirection of blood flow to blood vessels in the walls (lamina propria, submucosa) of the upper gastric and lower oesophageal regions resulting in the development of oesophageal varices. 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.

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
Based on the published study, 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 of terlipressin follows a two-compartment model with a rapid distribution phase.

Absorption
Terlipressin is administered by the intravenous route resulting in instant systemic exposure.

Distribution
In patients with liver cirrhosis with or without hepatorenal syndrome the mean distribution volume was reported in the range 0.2 to 0.5 l/kg in two clinical trials.

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 terminal elimination half-life of terlipressin is approximately 40 minutes in patients with liver cirrhosis with and without hepatorenal syndrome and the mean clearance was reported in the range 5 to 9 ml/kg/min in two clinical trials.

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

6.0 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- Sodium chloride
- Glacial acetic acid
- Sodium acetate
- Water for injections

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must no be mixed with other medicinal products except for those stated in section Other handling information.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in a refrigerator (2°C-8°C). Keep vials in the outer carton in order to protect from light.

6.5 Nature and contents of container
Type I glass vial with chlorobutyl rubber stopper and 20 mm aluminium-plastic overseal.
The vial contains terlipressin acetate 1 mg in 8.5 ml of solution for injection.
Pack size: 10 vials per box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product
Any unused drug or waste material should be disposed of in accordance with local requirements.

6.7 Other Handling Information
For intravenous infusion:
The terlipressin daily dose can be diluted using aseptic technique in up to 250mL of sodium chloride 9mg/mL (0.9%) or glucose 50mg/mL (5%) before administration. The diluted solution is stable for up to 24 hours at 25°C.

7. PRODUCT REGISTRATION HOLDER
Pharmaniaga Marketing Sdn Bhd (198401005734)
No.7 Lorong Keluli 1B, Kawasan Perindustrian Bukit
Raja Selatan, Seksyen 7, Shah Alam,
40000, Selangor

8. MANUFACTURED BY
Hainan Poly Pharm.Co., Ltd.
Guilinyang Economic Development Area,
Haikou, Hainan Province,
571127, China.

9. DATE OF REVISION
26/05/2025