SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terlipressin Acetate 1 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 8.5 ml solution 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 ampoule contains 1.33 mmol (30.6 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bleeding oesophageal varices

4.2 Posology and method of administration

The administration of terlipressin serves the emergency care for acute bleeding oesophageal varices until endoscopic therapy is available. Afterwards the administration of terlipressin for the treatment of oesophageal varices is usually an adjuvant therapy to the endoscopic haemostasis.

Adults
Initially 1-2 mg terlipressin acetate (equivalent to 1-2 ampoules of Terlipressin Acetate 1 mg solution for injection) are administered.

Depending on the patient's body weight the dose can be adjusted as follows:

- weight less than 50 kg: 1 mg (1 ampoule of 8.5 ml)
- weight 50 kg to 70 kg: 1.5 mg (1.5 ampoules of 8.5 ml)
- weight exceeding 70 kg: 2 mg (2 ampoules of 8.5 ml).

After the initial injection, the dose can be reduced to 1 mg every 4 to 6 hours.

The approximate value for the maximum daily dose of Terlipressin Acetate 1 mg solution for injection is 120 µg/kg body weight.

The therapy is to be limited to 2 – 3 days in adaptation to the course of the disease.

Terlipressin Acetate 1 mg solution for injection

is injected intravenously and should be given during the period of one minute.

Elderly
Terlipressin Acetate 1 mg solution for injection should only be used with caution in patients over 70 years (see section 4.4)

Children and adolescents
Terlipressin Acetate 1 mg solution for injection is not recommended in children and adolescents due to insufficient experience on safety and efficacy (see section 4.4)

Renal insufficiency
Terlipressin Acetate 1 mg solution for injection should only be used with caution in patients with chronic renal failure (see section 4.4).

Hepatic insufficiency
A dose adjustment is not required in patients with liver failure

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In principle the use of the product should be confined to specialist supervision in units with facilities for regular monitoring of the cardiovascular system, haematology and electrolytes.

Terlipressin Acetate 1 mg solution for injection should only be used with caution and under strict monitoring of the patients in the following cases:

- septic shock
- bronchial asthma, respiratory deficiencies
- uncontrolled hypertension
- cerebral or peripheral vascular diseases
- cardiac arrhythmias
- cardiac insufficiency
- coronary deficiencies or previous myocardial infarction
- chronic renal insufficiency
- elderly patients > 70 years as experience is limited in this group
- pregnancy (see section 4.6).

Also hypovolaemic patients often react with an increased vasoconstriction and atypical cardiac reactions.
Due to the weak antidiuretic effect of terlipressin (only 3% of the antidiuretic effect of native vasopressin) especially patients with already disturbed electrolyte metabolism should be monitored for a possible hyponatraemia and hypokalaemia.

In emergency situations which require an immediate treatment before sending the patient to a hospital, symptoms of hypovolaemia have to be considered.

Terlipressin has no effect on arterial bleeding.

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

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

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, electrolytic anormalities, concomitant medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that can cause hypokalaemia or hypomagnesemia (e.g. some diuretics) (see section 4.5).

Special populations:
Particular caution should be exercised in the treatment of children, adolescents and elderly patients, as experience is limited and there is no data available regarding dosage recommendation in these special patient categories.

This medicinal product contains 30.6 mg sodium per ampoule, equivalent to 1.53% 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 interaction

Terlipressin increases the hypotensive effect of non-selective β-blockers on the portal vein. The reduction in heart rate and cardiac output caused by the treatment can be attributed to the inhibition of the reflexogenic activity of the heart through the vagus nerve as a result of increased blood pressure. Concomitant treatment with drugs known to induce bradycardia (e.g. propofol, sufentanil) can cause severe bradycardia.

Terlipressin can trigger ventricular arrhythmias including "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
The use of terlipressin is not recommended during pregnancy as it 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 has been shown in rabbits after treatment with terlipressin (see section 5.3).

Terlipressin Acetate 1 mg solution for injection should therefore only be used at vital indication on a case by case decision especially in the first trimester, when bleeding cannot be controlled with endoscopic therapy.

Breast-feeding
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 breast-feeding to the child and the benefit of terlipressin therapy to the woman.

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

Treatment of bleeding oesophageal varices with Terlipressin Acetate 1 mg solution for injection (1 mg intravenously and more) may be accompanied by the adverse reactions in Table 1.

The assessment of undesirable effects is based on the following frequencies:

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
Very rare: < 1/10,000
Frequency not known: cannot be estimated from the available data

Table 1. Adverse reactions reported with treatment of bleeding oesophageal varices with terlipressin

MedDRA system organ class	**Adverse reaction (preferred term)**
Metabolism and nutrition disorders	
uncommon	hyponatraemia if fluid not monitored
very rare	hyperglycaemia
Nervous system disorders	
common	headache
uncommon	triggering of a convulsive disorder
very rare	stroke
Cardiac disorders	
common	ventricular and supra-ventricular arrhythmia, bradycardia, signs of ischaemia in the ECG
uncommon	angina pectoris, acute hypertension rise, in particular in patients already suffering from hypertension (generally, it decreases spontaneously), atrial fibrillation, ventricular extrasystoles, tachycardia, chest pain, myocardial infarction, fluid overload with pulmonary oedema, cardiac failure, Torsade de Pointes
very rare	myocardial ischemia

Vascular disorders	
common	hypertension, hypotension, peripheral ischaemia, peripheral vasoconstriction, facial pallor
uncommon	intestinal ischaemia, peripheral cyanosis, hot flushes
Respiratory, thoracic and mediastinal disorders	
uncommon	pain in the chest, bronchospasm, respiratory distress, respiratory failure
rare	dyspnoea
Gastrointestinal disorders	
common	transient abdominal cramps, transient diarrhoea
uncommon	transient nausea, transient vomiting
Skin and subcutaneous tissue disorders	
common	paleness
uncommon	lymphangitis
not known	skin necrosis unrelated to the site of administration
Reproductive system and breast disorders	
common	abdominal cramps (in women)
Pregnancy, puerperium and perinatal conditions	
uncommon	uterine hypertonus, uterine ischemia
not known	uterine constriction, decreased uterine blood flow
General disorders and administration site conditions	
uncommon	injection site necrosis

During clinical trials and post-marketing experience, several cases of QT interval prolongation and ventricular arrhythmias including "Torsade de pointes" have been reported (see sections 4.4 and 4.5).

During post-marketing experience, several cases of cutaneous ischemia and necrosis unrelated to the injection site have been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the United Kingdom, Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The recommended dose should not be exceeded in any case, since the risk of severe circulatory adverse effects is dose-dependent.
An acute hypertensive crisis, especially in patients with recognized hypertension, can be controlled with a vasodilator-type alpha-blocker, e.g. 150 micrograms clonidine intravenously.
Bradycardia requiring treatment should be treated with atropine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic hormonal preparations, posterior pituitary lobe hormones, vasopressin and analogues

ATC code: H 01 BA 04.

Terlipressin inhibits portal hypertension with simultaneous reduction of blood circulation in portal vessels. Terlipressin contracts smooth oesophageal muscle with consecutive compression of oesophageal varices.

The inactive pre-hormone terlipressin slowly releases bioactive lysine-vasopressin. Metabolic elimination takes place concomitantly and within a period of 4-6 hours. Therefore, concentrations remain continuously above the minimal effective dose and below toxic concentrations.

Specific effects of terlipressin are assessed as follows:
Gastrointestinal system:
Terlipressin increases the tone of vascular and extravascular smooth muscle cells. The increase in arterial vascular resistance leads to decrease of splanchnic hypervolemia. The decrease of the arterial blood supply leads to reduction of pressure in the portal circulation. Intestinal muscles contract concomitantly which increases intestinal motility. The muscular wall of the esophagus also contracts which leads to closure of experimentally induced varices.

Kidneys:
Terlipressin has only 3% antidiuretic effect of the native vasopressin. This residual activity is of no clinical significance. Renal blood circulation is not significantly effected in normovolemic condition. Renal blood circulation is increased, however, under hypovolemic condition.

Blood pressure:
Terlipressin induces a slow haemodynamic effect which lasts 2-4 hours. Systolic and diastolic blood pressure increase mildly. More intense blood pressure increase has been observed in patients with renal hypertension and general blood vessel sclerosis.

Heart:
All studies reported that no cardio-toxic effects were observed, not even under the highest dose of terlipressin. Influences on the heart, such as bradycardia, arrhythmia, coronary insufficiency, occur possibly because of reflex or direct vascular constrictive effects of terlipressin.

Uterus:
Terlipressin causes significant decrease in myometrial and endometric blood flow.

Skin:
The vasoconstrictive effect of terlipressin causes significant decrease in blood circulation of the skin. All studies reported obvious paleness on face and body.

In conclusion, the main pharmacological properties of terlipressin are its haemodynamic effects and its effects on smooth muscle. The centralization effect under hypovolemic condition is a desired side effect in patients with bleeding oesophageal varices.

5.2 Pharmacokinetic properties

After bolus intravenous injection terlipressin elimination follows second order kinetics. Plasma half-life was calculated as 8-12 minutes during the distribution phase (0-40 minutes) and 50-80 minutes during the elimination phase (40-180 minutes). The release of lysine-vasopressine is maintained for at least 180 minutes. Due to cleavage of the glycyl rests from terlipressin lysine-vasopressin is slowly released and reaches maximal concentrations after 120 minutes. Urine contains only 1% of the injected terlipressin, which indicates almost complete metabolism by endo- and exopeptidases of liver and kidneys.

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 doses relevant to humans, the only effects observed in animals were those attributed to the pharmacological activity of terlipressin.

Adverse reactions observed in animal studies with possible relevance to clinical use were as follows:

Due to its pharmacological effect on smooth muscles Terlipressin Acetate 1 mg solution for injection may induce abortion in the first trimester.

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

No carcinogenicity studies have been performed with terlipressin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Glacial acetic acid
Sodium acetate trihydrate
Water for injection

6.2 Incompatibilities

- Alkaline solutions
- Reducing sugars solutions

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store in a refrigerator (2-8°C). Keep in the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

Terlipressin Acetate 1 mg solution for injection is packed in 10 ml clear Type I glass ampoules containing 8.5 ml of solution with 1 mg terlipressin acetate.

This medicine is packed into one carton with 5 ampoules with 8.5 ml of solution.

6.6 Special precautions for disposal and other handling

Only for intravenous injection.

Once opened the medicine should be used immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Flynn Pharma Ltd
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8. MARKETING AUTHORISATION NUMBER(S)

PL 13621/0075

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/10/2021

10. DATE OF REVISION OF THE TEXT

To be completed on approval