# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Terlipressin Altan 1 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 8.5 ml solution contains 1 mg terlipressin acetate.

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

Bleeding oesophageal varices.
Treatment of type I hepatorenal syndrome.

### 4.2 Posology and method of administration

1) Oesophageal varices bleeding

Unless otherwise prescribed, initially IV injection of 1-2 mg terlipressin acetate, equivalent to 1-2 ampoules of Terlipressin Altan 1 mg, is slowly administered to adults. The maintenance dose is 1 mg terlipressin acetate, equivalent to 1 ampoule of Terlipressin Altan 1 mg after 4-6 hours. The standard value of the maximum daily dose of Terlipressin Altan 1 mg is 120-150 ug/kg body weight. For an adult person of 70 kg body weight, this corresponds to a dose of 8-10 ampoules per day, to be administered in 4-hour intervals.

2) In type 1 hepatorenal syndrome:

3 to 4 mg every 24 hours as 3 or 4 administrations.
In the absence of any reduction of the serum creatinine after 3 days of treatment, cessation of Terlipressin Altan 1 mg treatment is advised.
In the other cases, Terlipressin Altan 1 mg treatment is to be pursued until the obtaining either of a serum creatinine less than 130 µmol/litre or of a drop of at least 30 % in the serum creatinine with respect to the value measured at the time of diagnosis of hepatorenal syndrome. The standard average duration of treatment is 10 days.

**Special Populations**

*Elderly patients*

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**

IV injection

### 4.3 Contraindications

Hypersensitivity to terlipressin or any other excipient of the product.
Contraindicated in pregnancy.

### 4.4 Special warnings and precautions for use

**Cardiac, pulmonary and vascular disease**

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

Caution should be exercised in treating patients with hypertension, recognised heart disease, renal dysfunction, cerebral or peripheral vascular disease, asthma or respiratory failure.

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

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

Prior to use of terlipressin for hepatorenal syndrome, it must be ascertained that the patient has an acute functional renal failure and this functional renal failure does not respond to a suitable plasma expansion therapy.
Paediatric population and elderly patients: Particular caution should be exercised in the treatment of children and elderly patients, as experience is limited in these groups.
There is no data available regarding dosage recommendation in these special patient categories.

This medicinal product contains 1.33 mmol (30.6 mg) sodium per ampoule of 8.5 ml. To be taken into consideration by patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

Pregnancy
Treatment with Terlipressin Altan 1 mg during pregnancy is contraindicated (see sections 4.3 and 5.3). Terlipressin Altan 1 mg has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. Terlipressin Altan 1 mg may have harmful effects on pregnancy and foetus.
Spontaneous abortion and malformation have been shown in rabbits after treatment with Terlipressin Altan 1 mg.
Brest -feeding
It is not known whether Terlipressin Altan 1 mg is excreted in human breast milk. The excretion of Terlipressin Altan 1 mg 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 Altan 1 mg should be made taking into account the benefit of breast-feeding to the child and the benefit of Terlipressin Altan 1 mg therapy to the woman.

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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 commonly reported undesired effects in clinical trials are paleness, increased blood pressure, abdominal pain, nausea, diarrhoea, and headache.

Tabulated list of adverse reactions

| MedDRA System organ class | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare ( ≥1/10,000 to <1/1,000) |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | Hyponatraemia | |
| **Nervous system disorders** | Headache | | |
| **Cardiac disorders** | Bradycardia | Atrial fibrillation<br>Ventricular extrasystoles<br>Tachycardia<br>Myocardial infarction<br>Torsade de pointes<br>Cardiac failure<br>cyanosis | |
| **Vascular disorders** | vasoconstriction<br>Peripheral ischemia<br>pallor<br>Hypertension | Hot flush | |
| **Respiratory, thoracic and mediastinal disorders** | | Respiratory distress<br>Pulmonary oedema<br>Respiratory failure | Dyspnoea |
| **Gastrointestinal disorders** | abdominal pain<br>diarrhoea | nausea<br>Intestinal ischemia<br>vomiting | |
| **Skin and subcutaneous tissue disorders** | | Skin necrosis | |
| **Pregnancy, puerperium and perinatal conditions** | | Uterine hypertonus<br>Uterine ischemia | |
| **General disorders and administration site disorders** | | Injection site necrosis<br>Chest pain | |

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

### 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.

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Elevated blood pressure in patients with hypertension can be controlled with clonidine 150 µg IV. Severe bradycardia should be treated with atropine

## 5. PHARMACOLOGICAL PROPERTIES

### 5.0 Pharmacotherapeutic group

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. 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 terlipressin acetate is more effective than 1 mg terlipressin acetate with a sustained effect throughout the treatment period (4 to 6 hours).

### 5.1 Pharmacodynamic properties

Terlipressin Altan 1 mg may be regarded as a circulating depot of lysine vasopressin. Following IV injection, three glycyl moieties are enzymatically cleaved from the N terminal to release lysine vasopressin.

The slowly released vasopressin reduces blood flow in the splanchnic circulation in a prolonged manner, thereby helping to control bleeding from ruptured oesophageal varices

### 5.2 Pharmacokinetoc properties

Terlipressin Altan 1 mg is administered by bolus IV injection. It shows a biphasic plasma level curve which indicates that a two compartment model can be applied. The half-life of elimination ($T_{½}$ β) is about 50-70 minutes.

Lysine vasopressin reaches **maximum** plasma levels about 1-2 hours following IV administration and has a duration of activity of 4-6 hours.

### 5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride, glacial acetate acid, sodium acetate trihydrate, 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

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

Store in a refrigerator (2-8ºC). Keep in the original package in order to protect from light.

### 6.5 Nature and contents of container

Terlipressin Altan 1 mg is packed in 10 ml type I glass ampoules containing 8.5 ml of solution with 1 mg terlipressin acetate.

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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**

Once opened the medicine should be used immediately.
For single use only. Discard any unused solution.

**7. MANUFACTURER**

Altan Pharmaceuticals S.A.
Avda.de la Constitución 198-199, Polígono Industrial Monte Boyal
45950 Casarrubios del Monte (Toledo), Spain

**8. REGISTRATION HOLDER**

Propharm Ltd., P.O.Box 4046
Ben Gurion 23, Zichron Yaacov, 30900

**9 REGISTRATION NUMBER**

164-13-35448-00

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