Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Variquel Solution 0.2mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of injection solution contains 1 mg terlipressin acetate corresponding to 0.85 mg terlipressin.

Each ml contains 0.2 mg terlipressin acetate corresponding to 0.17 mg terlipressin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear colourless aqueous solution with a pH of 5.7 – 6.3 and an osmolality of 270 – 330 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of bleeding oesophageal varices.

Emergency treatment of hepatorenal syndrome (type I), characterised by spontaneous acute renal failure in patients with severe cirrhosis and ascites.

4.2 Posology and method of administration

For intravenous use only. The solution should be inspected prior to administration. Do not use Variquel Solution if it contains particles or is discoloured.

Method of administration
For administration, the required volume should be extracted from the vial with a syringe and then slowly administered intravenously over a period of at least one minute.

Posology
Adults

Oesophageal varices bleeding
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.

Initial dose: The recommended initial dose is 1 to 2 mg terlipressin acetate[#] (equivalent to 5 to 10 ml of solution) administered by intravenous injection over a period of at least one minute.

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

- weight less than 50 kg:	1 mg terlipressin acetate (5 ml)
- weight 50kg to 70 kg:	1.5 mg terlipressin acetate (7.5 ml)
- weight exceeding 70 kg:	2 mg terlipressin acetate (10 ml).

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

[#] 1 to 2 mg terlipressin acetate corresponding to 0.85 to 1.7 mg terlipressin

The approximate value for the maximum daily dose of Variquel Solution is 120 µg/kg body weight.

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

Hepatorenal syndrome
Treatment in adults is usually started with a dose of 1 mg terlipressin acetate[#] (5 ml of solution) at 4 to 6-hour intervals. The dose can be increased to a maximum of 2 mg terlipressin acetate[#] (10 ml of solution) every 4 hours if the serum creatinine does not decrease by at least 25% after 3 days of treatment.
[#] 1 mg terlipressin acetate corresponding to 0.85 mg terlipressin ; 2 mg terlipressin acetate corresponding to 1.7 mg terlipressin
The treatment is continued until the serum creatinine has dropped below 1.5 mg/dl (133 µmol/l). In patients with a partial response (serum creatinine does not drop below 133 µmol/l) or in patients whose serum creatinine does not decrease, treatment should be stopped within 14 days.
In most clinical studies supporting the use of terlipressin for the treatment of hepatorenal syndrome, human albumin was administered simultaneously at a dosage of 1 g/kg of body weight on the first day and afterwards at a dosage of 20 - 40 g/day.

The usual duration of treatment of hepatorenal syndrome is 7 days, and the maximum recommended duration is 14 days.

Elderly patients
Variquel Solution should be used with caution in patients over 70 years of age (see section 4.4). There are no dosage recommendations for the elderly.

Paediatric population
The safety and efficacy of Variquel Solution in children and adolescents has not yet been established. No data are available. Variquel Solution is not recommended in children and adolescents (see section 4.4).

Renal insufficiency
Variquel Solution 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

Variquel Solution should be used with caution and under strict monitoring of the patients in the following cases:

- septic shock
- bronchial asthma, respiratory deficiencies
- uncontrolled hypertension
- cerebral, coronary and peripheral vascular diseases (e.g. advanced arteriosclerosis)
- pre-existing seizures (seizures)
- cardiac arrhythmias
- history of ischemic cardiovascular disease because terlipressin can induce ischemia
- coronary deficiencies or previous myocardial infarction
- chronic renal insufficiency
- elderly patients over 70 years of age as experience is limited in this group
- pregnancy (see section 4.6).

Hypovolaemic patients often react with an increased vasoconstriction and atypical cardiac reactions.

Terlipressin has a weak antidiuretic effect (only 3% of the antidiuretic effect of native vasopressin) therefore patients with a history of disturbed electrolyte metabolism should be monitored for a possible hyponatraemia and hypokalaemia.

In principle the use of the product should be confined to specialist supervision. Regular checks of blood pressure, ECG, heart rate, sodium and potassium serum levels and fluid balance are required during treatment.

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

Terlipressin has no effect on arterial bleeding.

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

Skin Necrosis:
During post-marketing experience several cases of cutaneous ischemia and necrosis unrelated to the injection site (see section 4.8) have been reported. 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 abnormalities, 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).

This medicinal product contains less than 1mmol (23 mg) of sodium per 5 ml, i.e. essentially "sodium-free".

Special populations
Particular caution should be exercised in the treatment of children, adolescents and elderly patients, as experience is limited and there are no safety and efficacy data available regarding dosage recommendation in this population.

4.5 Interaction with other medicinal products and other forms of interactions

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).

Variquel Solution 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.

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 breastfed child cannot be excluded.

A decision should be made on whether to discontinue breast-feeding or to discontinue/abstain from terlipressin therapy taking into account the benefit of breast-feeding to the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most common side effects reported in clinical studies (frequency 1-10%) are paleness, high blood pressure, abdominal pain, nausea, diarrhoea and headache.
The antidiuretic effects of terlipressin can cause hyponatremia if the fluid balance is not controlled.

Tabulated list of adverse reactions
The following frequencies are used to evaluate side effects:
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)
Not known (frequency cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse Reaction (Preferred Term)**
Metabolism and nutrition disorders	
common (≥1/100 to <1/10)	hyponatraemia if fluid not monitored
Nervous system disorders	
common (≥1/100 to <1/10)	headache
uncommon (≥1/1,000 to <1/100)	triggering of a convulsive disorder
very rare (<1/10,000)	stroke
Cardiac disorders	
common (≥1/100 to <1/10)	ventricular and supra-ventricular arrhythmia, bradycardia, signs of ischaemia in the ECG
uncommon (≥1/1,000 to <1/100)	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 (<1/10,000)	myocardial ischemia
Vascular disorders	
common (≥1/100 to <1/10)	hypertension, hypotension, peripheral ischaemia, peripheral vasoconstriction, pallor
uncommon (≥1/1.000 to <1/100)	intestinal ischaemia, peripheral cyanosis, hot flushes
Respiratory, thoracic and mediastinal disorders	
uncommon (≥1/1,000 to <1/100)	painful breathing, bronchospasm, respiratory distress, respiratory failure, respiratory arrest
rare (≥1/10,000 to <1/1,000)	dyspnoea
Gastrointestinal disorders	
common (≥1/100 to <1/10)	abdominal cramps, diarrhoea, nausea
uncommon (≥1/1,000 to <1/100)	vomiting
Skin and subcutaneous tissue disorders	
uncommon (≥1/1,000 to <1/100)	lymphangitis, skin necrosis unrelated to the site of administration
Pregnancy, puerperium and perinatal conditions	
uncommon (≥1/1,000 to <1/100)	uterine hypertonus, uterine ischemia
Reproductive system and breast disorders	
common (>1/100 to <1/10)	abdominal cramps (in women)
General disorders and administration site conditions	
uncommon (≥1/1,000 to <1/100)	injection site necrosis

Description of selected adverse reactions

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 HPRA Pharmacovigilance Website: www.hpra.ie.

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 microgram 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: H01BA04

Terlipressin has low pharmacological activity but is converted to the active lysine vasopressin by enzyme cleavage.

Doses of 0.85 mg terlipressin (corresponding to 1 mg terlipressin acetate) and 1.7 mg terlipressin (corresponding to 2 mg terlipressin acetate) reduce portal vein pressure and cause a noticeable vasoconstriction. Lowering the portal pressure and reducing the blood flow of the azygos vein is dose dependent. The effect of the low dose wears off after 3 hours, while hemodynamic data show that 1.7 mg terlipressin is more effective than 0.85 mg, since the higher dose shows a more reliable effect over the entire treatment period (4 hours).

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:

<u>Gastrointestinal system:</u>
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 oesophagus also contracts which leads to closure of experimentally induced varices.

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

<u>Blood pressure:</u>
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

The mean plasma half-life of terlipressin is 24 minutes. 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-vasopressin is maintained for at least 180 minutes. Due to cleavage of the glycyl groups 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

Non-clinical data reveal no special hazard for humans based on conventional studies of single- and repeat-dose toxicity, and genotoxicity. No carcinogenicity studies have been performed with terlipressin.
At doses relevant to humans, the only effects observed in animals were those attributed to the pharmacological activity of terlipressin.

Animal pharmacokinetic data are not available to compare with the plasma concentrations in humans at which these effects have occurred, however, since administration is intravenous, substantial systemic exposure can be assumed.
Due to its pharmacological effect on smooth muscles Variquel Solution 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Sodium acetate trihydrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened: 3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Keep the vial in the outer carton in order to protect from light.
From a microbiological point of view, after first opening, the product should be used immediately.

6.5 Nature and contents of container

Terlipressin Solution is supplied to the market in colourless glass type I vials, closed with bromobutyl rubber stopper and sealed with aluminium flip-off cap (green).
Each vial contains 5 ml of solution.

Pack sizes: 5 x 5ml

6.6 Special precautions for disposal and other handling

No special requirements.
For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharma (Ireland) Limited
United Drug Distributors, United Drug House
Magna Business Park, Magna Drive
Citywest
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA2325/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25th October 2013
Date of Last Renewal: 30th March 2016

10 DATE OF REVISION OF THE TEXT

September 2021