1 PRODUCT NAME

VARIQUEL, 1mg/ 5mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 5mL contains 1mg terlipressin acetate (equivalent to 0.85mg 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

VARIQUEL 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

Bleeding Oesophageal Varices

An intravenous injection of 2mg 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 1mg terlipressin acetate every 4 hours in patients with a body weight of less than 50kg or when necessitated by adverse effects.

Type 1 Hepatorenal Syndrome

3-4mg terlipressin acetate every 24 hours as 3 or 4 administrations.
If serum creatinine does not decrease at least 25% after 3 days, the dose can be increased in a stepwise manner up to a maximum of 2mg terlipressin acetate every 4 hours.
In the other cases, terlipressin treatment is to be pursued until the obtaining either of a serum creatinine less than 130µmol/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.

VARIQUEL must only be administered intravenously.

4.3 Contraindications

- Pregnancy
- Septic shock with low cardiac output
- Hypersensitivity to terlipressin or any other excipients of the product listed in section 6.1.
- Contraindicated in patients with current or recent (within the last 3 months) ischaemic cardiovascular disease.

4.4 Special warnings and precautions for use

Cardiac, pulmonary and vascular disease

During treatment regular controls 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 or recognised heart disease. Caution should also be exercised in patients with a history of ischaemic cardiovascular disease since terlipressin may induce ischaemia.

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 intravenously.

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).

Acute kidney injury
Prior to treatment of type 1 hepatorenal syndrome, other types of acute kidney injury should be ruled out.

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

4.5 Interaction with other medicines 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 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.

Breastfeeding
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 commonly reported undesirable effects in clinical trials (frequency 1-10%) are paleness, increased blood pressure, abdominal pain, nausea, diarrhoea and headache.

The antidiuretic effect of terlipressin may cause hyponatraemia unless fluid balance is controlled.

Tabulated summary of adverse reactions

System Organ Class Disorder	COMMON (≥1/100 to <1/10)	UNCOMMON (≥1/1,000 to <1/100)	RARE (≥1/10,000 to <1/1,000)
Metabolism		Hyponatraemia	
Nervous system	Headache		
Cardiac	Bradycardia	Atrial Fibrillation Ventricular extrasystoles Tachycardia Myocardial Infarction Torsade de pointes Cardiac failure Cyanosis	
Vascular	Vasoconstriction Peripheral ischaemia Pallor Hypertension	Hot flushes	
Respiratory		Respiratory distress Respiratory failure Pulmonary oedema	Dyspnoea
Gastrointestinal	Abdominal cramps Diarrhoea	Nausea Vomiting Intestinal ischaemia	
Skin and subcutaneous		Skin necrosis	
Pregnancy, puerperium and perinatal conditions		Uterine hypertonus Uterine ischaemia	
General disorders and administration site disorders		Injection site necrosis Chest pain	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 150mcg 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.

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

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

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). The vials are stored 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

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

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246

Telephone: (09) 815 2664.

9 DATE OF FIRST APPROVAL

28 January 2021

10 DATE OF REVISION OF THE TEXT

27 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change of PO Box details Addition of trade mark information.