

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Variquel 1 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains:

1 mg terlipressin acetate equivalent to 0.85 mg terlipressin.

1 ml of reconstituted solution contains 0.2 mg terlipressin acetate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

White to off white solid powder and a 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 vials of Variquel) are administered.

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

- Weight less than 50 kg: 1 mg.

- Weight 50 kg to 70 kg: 1.5 mg.

- Weight exceeding 70 kg: 2 mg.

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 Variquel is 120 µg/kg body weight.

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

Variquel is dissolved with the accompanying solvent and is applied intravenously. The intravenous injection should be given during the period of one minute. For further dilution see section 6.6.

Elderly

Variquel should only be used with caution in patients over 70 years (see section 4.4).

Children and adolescents

Variquel is not recommended in children and adolescents due to insufficient experience on safety and efficacy (see section 4.4)

Renal insufficiency

Variquel 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.

4.4 Special warnings and precautions for use

Variquel 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
- 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 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.

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.

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 hypomagnesaemia (e.g. some diuretics) (see section 4.5).

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.

After reconstitution with the accompanying solvent, this medicinal product contains less than 1 mmol (23 mg) of sodium per 5 ml, i.e. essentially "sodium-free".

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 hypomagnesaemia (e.g. some diuretics).

4.6 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 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 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

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

very common ($\geq 1/10$)

common ($\geq 1/100$ to $< 1/10$)

uncommon ($\geq 1/1.000$ to $< 1/100$)

rare ($\geq 1/10.000$ to $< 1/1.000$)

very rare ($< 1/10.000$)

not known (cannot be estimated from the available data)

Treatment of bleeding oesophageal varices with Variquel (1 mg intravenously and more) may be accompanied by the following adverse reactions:

Metabolism and nutrition disorders

Uncommon: hyponatraemia

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

Very rare: myocardial ischemia

Not known: cardiac failure, Torsade de Pointes

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

Not known: uterine constriction, decreased uterine blood flow

General disorders and administration site conditions:

Uncommon: local cutaneous 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).

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 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 endometrial 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-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

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 Variquel 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

Each vial of powder contains:
Mannitol
Acetic acid (for pH adjustments)

Each solvent ampoule contains:
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 18 months
After reconstitution with solvent ampoule: Use immediately.
From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light. For storage of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:

Colourless, type I glass vials, closed with bromobutyl rubber stopper and sealed with aluminium flip-off cap
Each vial contains 11 mg powder.

Solvent:

Colourless, type I glass ampoules, sealed by fusion
Each ampoule contains 5 ml solvent.

Pack sizes:

1 vial with powder and 1 ampoule of solvent
5 vials with powder and 5 ampoules of solvent

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitute the powder only in the solvent provided.

Preparation of injection

The entire contents of the solvent ampoule should be slowly added to the powder vial and the vial rolled gently until the powder is completely dissolved. The powder should dissolve within 10 seconds. A clear colourless solution results.

A further dilution to 10 ml with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection is possible.

For single use only. Discard any unused solution.

The solution should be inspected visually for particles and discolouration prior to administration.

Do not use Variquel if you notice

- that the powder does not dissolve in the accompanying solvent
- that the solution discolours after dissolving the powder.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 13538/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/06/2009

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August 2010