

Package leaflet: Information for the user

Variquel[®], 0.2mg/ml, solution for injection

Terlipressin acetate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Variquel is and what it is used for
2. What you need to know before you use Variquel
3. How to use Variquel
4. Possible side effects
5. How to store Variquel
6. Contents of the pack and other information

1. What Variquel is and what it is used for

Variquel contains the active ingredient terlipressin which is a synthetic pituitary hormone (this hormone is usually produced by the pituitary gland found in the brain).

It will be given to you by injection into a vein.

Variquel is used for the treatment of:

- Severe or life-threatening bleeding of dilated veins (varices) in the food pipe and stomach. Terlipressin works by narrowing the blood vessels in this area, helping to control bleeding from varices of the food pipe and stomach when it occurs.
- Emergency treatment of a type of kidney failure in patients with severely impaired liver function (type 1 hepatorenal syndrome). Terlipressin works by reducing pressure in the veins of the liver (portal venous pressure) in patients with high blood pressure in the vein that carries blood to the liver (portal hypertension) and also contributes to improve blood circulation in the kidney helping to restore renal function.

2. What you need to know before you use Variquel

Do not use Variquel:

- if you are allergic to terlipressin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before using Variquel.

If you are able, please tell the doctor if you have any of the conditions below:

- a severe infection known as septic shock
- bronchial asthma or other conditions that affect your breathing

- uncontrolled high blood pressure, insufficient blood circulation in the heart vessels (e.g. angina), coronary insufficiency, have previously had a heart attack (myocardial infarction), or you have hardening of the arteries (arteriosclerosis)
- seizure disorder (suffering from fits)
- irregular heart beats (cardiac arrhythmias) or a history of QT interval prolongation (disturbance of heart rhythm)
- poor blood circulation to your brain (e.g. you have had a stroke) or to your limbs (peripheral vascular disease)
- impaired kidney function (renal insufficiency)
- disturbances in the level of salt (electrolytes) in your blood
- reduced amount of fluid in your circulation or have already lost a large amount of blood
- are over the age of 70 years
- are pregnant

Children and adolescents

Variquel is not recommended for use in children and adolescents due to insufficient experience.

Other medicines and Variquel

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescriptions.

Please inform your doctor immediately if you take any of the following medicines:

-drugs that have an effect on your heart rate (e.g. beta-blockers, sufentanil or propofol)

-drugs that can trigger irregular beating of the heart (arrhythmia) such as the following:

- anti-arrhythmic drugs known as Class IA (quinidine, procainamide, disopyramide) and Class III (amiodarone, sotalol, ibutilide, dofetilide)
- erythromycin (an antibiotic)
- antihistamines (mainly used to treat allergies but also found in certain cough and cold remedies)
- tricyclic antidepressants used to treat depression
- medicines that may alter the level of salt or electrolytes in your blood, particularly diuretics (water tablets used to treat high blood pressure and heart failure)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Variquel should only be used during pregnancy if it is vital to treat your condition.

It is not known if Variquel is present in breast milk, therefore the possible effects on your baby are unknown. You should discuss the potential risk to your baby with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. However, if you feel unwell after receiving the injection, do not drive or operate machinery.

Variquel contains Sodium

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

3. How to use Variquel

This medicine will always be given to you by a doctor into your vein. The doctor will decide the most appropriate dose for you and your heart and blood circulation will be continuously monitored during the injection. Please ask your doctor for further information regarding its use.

Use in adults

Bleeding of dilated veins (varices) in the food pipe and stomach:

Initially 1-2 mg terlipressin acetate (5-10 ml of Variquel) is given by injection into your vein. Your dose will depend on your body weight.

After the initial injection, your dose may be reduced to 1 mg terlipressin acetate (5 ml of Variquel) every 4 to 6 hours.

The maximum dose you can receive each day is approximately 120 micrograms/kg body weight.

The therapy should be limited to 2-3 days in line with the course of the disease.

Hepatorenal syndrome:

Treatment in adults is usually started with a dose of 1 mg terlipressin acetate (5 ml of Variquel) at 4 to 6-hour intervals.

The dose can be increased to a maximum of 2 mg terlipressin acetate (10 ml of Variquel) every 4 hours if the serum creatinine does not decrease by at least 25% after 3 days of treatment. Treatment is continued until normal kidney function is restored, up to 14 days.

Method and route of administration:

Variquel is injected intravenously (directly into the bloodstream).

Use in the elderly

If you are over 70 years of age speak with your doctor before you receive Variquel.

Use in patients with kidney problems

Variquel should be used with caution in patients with long standing kidney failure.

Use in patients with liver problems

No dose adjustment is required in patients with liver failure.

Use in children and adolescents

Variquel is not recommended for use in children and adolescents due to insufficient experience.

If you use more Variquel than you should

As this medicine is given by a healthcare professional, then it is unlikely you will be given more than the recommended dose. If you are given too much then you may have a rapid increase in your blood pressure (this will be noticed during the continuous monitoring), especially if you already suffer with high blood pressure. If this happens then you will be given another medicine called an alpha blocker (e.g. clonidine) to control your blood pressure.

If you experience light-headedness, dizziness, or feeling faint, tell your doctor because these could be signs of a low heart rate. This can be treated with another medicine called atropine.

If you forget to use Variquel

You will be given Variquel in hospital under the supervision of a doctor.

If you stop using Variquel

Your doctor will advise when it is time to stop receiving this medicine.

If you have any further questions on the use of this medicine, ask your doctor or nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects which need immediate attention:

In very rare cases, there may be severe side effects when you are given Variquel.

If you are affected by any of the following side effects, **please tell your doctor immediately** if you are able to. Your doctor should not give you any more Variquel.

- severe shortness of breath due to an asthma attack
- severe difficulty with or stopping breathing
- severe pain in the chest (angina, heart attack)
- severe and persistent irregular heart beats, including Torsade de Pointes
- dead skin around the injection site (necrosis)
- convulsions (seizure)
- kidney failure.

Other possible side effects:

Common (affects less than 1 in 10 people):

- too little sodium in the blood (hyponatraemia) if not checked regularly
- headache
- very slow heart rate (bradycardia)
- signs of insufficient blood circulation in the heart vessels in the ECG
- insufficient blood circulation in arms, legs and skin
- pale skin
- high or low blood pressure
- abdominal cramps
- nausea
- diarrhoea

Uncommon (affects less than 1 in 100 people)

- rapid heartbeat (tachycardia)
- chest pain
- excess fluid on the lungs
- heart muscle weakness (heart failure)
- reduced blood supply to the intestinal system
- bluish colouration of the skin or lips
- hot flushes
- painful breathing
- vomiting
- inflammation of the lymph vessels – seen as fine red streaks under your skin extending from the affected area to the armpit or groin and by fever, chills, headache, and muscle pain
- dead skin (necrosis) in areas other than at the injection site
- uterine cramps
- decreased blood flow to the uterus

Rare (affects less than 1 in 1000 people):

- shortness of breath

Very rare (affects less than 1 in 10,000 people):

- stroke

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme at

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Variquel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C).

Keep the vial in the outer carton in order to protect from light. The solution should be inspected visually for particles and discolouration prior to administration. Do not use this medicine if you notice discolouration. Do not throw away any medicines via wastewater or household waste. The doctor will dispose of this medicine. These measures will help protect the environment.

6. Contents of the pack and other information

What Variquel contains

- the **active** substance is terlipressin acetate. Each vial contains 1 mg terlipressin acetate in 5 ml solution, corresponding to 0.85 mg terlipressin. Each ml contains 0.2 mg terlipressin acetate, corresponding to 0.17 mg terlipressin per ml.

- the **other ingredients** are: glacial acetic acid, sodium acetate trihydrate and water for injections (see also end of section 2 for further information on sodium).

What Variquel looks like and contents of the pack

This medicine is supplied in a clear glass vial containing 5 ml of a clear, colourless solution.

This medicine is available in pack sizes of: 5 x 5ml

Marketing Authorisation Holder

Alliance Pharmaceuticals Limited
Avonbridge House, Bath Road
Chippenham, Wiltshire
SN15 2BB, United Kingdom

Manufacturer

BAG Health Care GmbH, Amtsgerichtsstraße 1-5, D-35423 Lich, Germany.

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium:	Variquel 0.2mg/ml, oplossing voor injectie
Denmark:	Variquel injektionsvæske, opløsning 0,2 mg/ml
France:	Variquel, 0.2 mg/mL, solution injectable
Germany:	Variquel Lösung, 0,2mg/ml, injektionslösung
Ireland:	Variquel Solution, 0.2mg/ml, solution for injection
Italy:	Stemflova 0.2mg/ml, soluzione iniettabile
Luxembourg:	Variquel Solution 0,2mg/ml, solution injectable
Netherlands:	Variquel Oplossing 0.17mg/ml, oplossing voor injectie
Portugal:	Variquel 1mg/5ml (0.2mg/ml), solução injetável
Sweden:	Variquel, 0,2mg/ml, injektionsvätska, lösning
UK:	Variquel, 0.2mg/ml, solution for injection

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The following information is intended for healthcare professionals only

Posology

Adults

Oesophageal varices bleeding

Initial dose: 1 to 2 mg terlipressin acetate[#] (equivalent to 5 to 10 ml solution) is 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 50 kg 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 is 120 micrograms/kg body weight.

The therapy is to be limited to 2 to 3 days depending on the response to treatment and 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 should only be used with caution in patients over 70 years. There are no dosage recommendations for the elderly.

Paediatric population

The safety and efficacy of Variquel in children and adolescents has not yet been established. No data are available. Variquel is not recommended in children and adolescents.

Renal insufficiency

Variquel should only be used with caution in patients with chronic renal failure.

Hepatic insufficiency

A dose adjustment is not required in patients with liver failure.

Preparation of the injection

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.

Store in a refrigerator (2°C-8°C).

Keep the vial in the outer carton to protect from light.

For single use only. Discard any unused solution.

From a microbiological point of view, after first opening, the product should be used immediately.

