

EU PACKAGE LEAFLET – EU-PI (PI/EU/ENGLISH)

BERIATE 250/500/1000/2000

Rev.: **02-May-2017** / Switch to 1-Box Version

Supersedes previous versions

Rev.: 15-DEC-2016 / Variation 090 comment IT

Rev.: 10-OCT-2016 / Adaptation to FVIII Core-SPC

PACKAGE INSERT: INFORMATION FOR THE USER

Beriate

Beriate 250 IU Powder and solvent for solution for injection or infusion
Beriate 500 IU Powder and solvent for solution for injection or infusion
Beriate 1000 IU Powder and solvent for solution for injection or infusion
Beriate 2000 IU Powder and solvent for solution for injection or infusion

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 further questions, ask your doctor or your 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Beriate is and what it is used for

What is Beriate?

Beriate is a powder plus the solvent. The made up solution is to be given by injection or infusion into a vein.

Beriate is made from human plasma (this is the liquid part of the blood) and it contains human coagulation Factor VIII. It is used to prevent or to stop bleedings caused by the lack of Factor VIII (haemophilia A) in the blood. It may also be used in the management of acquired Factor VIII deficiency.

What is Beriate used for?

Factor VIII is involved in blood clotting (coagulation). Lack of Factor VIII means that blood does not clot as quickly as it should and so there is an increased tendency to bleed. The replacement of Factor VIII with Beriate will temporarily repair the coagulation mechanisms.

2. What you need to know before you use Beriate

The following sections contain information that you and your doctor should consider before you use Beriate.

Do not use Beriate:

- If you are allergic (hypersensitive) to the human coagulation factor VIII or to any of the ingredients of this medicine (listed in section 6.).

Warnings and precautions:

Talk to your doctor or pharmacist before using Beriate.

- Allergic type hypersensitivity reactions are possible. Your doctor should inform you of the **early signs of hypersensitivity reactions**. These include hives, generalised skin rash, tightness of the chest, wheezing, fall in blood pressure and anaphylaxis (a serious allergic reaction that causes severe difficulty in breathing, or dizziness). **If these symptoms occur, you should stop the use of the product immediately and contact your doctor.**
- The formation of **inhibitors** (neutralising antibodies) to Factor VIII is a known complication of treatment and it means that the treatment stops working. If your bleeding is not being controlled with Beriate, tell your doctor immediately. You should be monitored carefully for the development of an inhibitor.
- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.
- If for the administration of Beriate you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Your doctor will consider carefully the benefit of treatment with Beriate compared with the risk of these complications.

Virus safety

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the production process that can inactivate or remove viruses or other pathogens. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the aids virus), hepatitis B virus and hepatitis C virus (inflammation of the liver) and for the non-enveloped viruses hepatitis A and parvovirus B19.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products (e.g. Factor VIII).

It is strongly recommended that every time that Beriate is given, you should record the date of administration, the batch number and the injected volume in your treatment diary.

Other medicines and Beriate:

- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
- Beriate must not be mixed with other medicinal products, diluents and solvents except for those that are recommended by the manufacturer (see section 6.)

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- During pregnancy and breast-feeding, Beriate should be given only if it is clearly indicated.
- No fertility data are available.

Driving and using machines

Beriate has no influence on the ability to drive and use machines.

Beriate contains sodium

Beriate contains up to 2.75 mg (0.12 mmol) sodium per ml. To be taken into consideration in patients on a controlled sodium diet.

3. How to use Beriate

Always use Beriate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Treatment of Haemophilia A should be started and supervised by a physician who is experienced in this type of disorder.

Dosage

The amount of Factor VIII you need and the duration of treatment will depend on several factors, such as your body weight, the severity of your disease, the site and intensity of bleeding or the need to prevent bleeding during an operation or investigation.

If you have been prescribed Beriate to use at home, your doctor will make sure that you are shown how to inject it and how much to use.

Follow the directions given to you by your doctor or hemophilia center nurse.

Use in children and adolescents

The dose is based on body weight and worked out in the same way as for adults.

If you use more Beriate than you should

No symptoms of overdose with FVIII have been reported.

If you forget to use Beriate

Proceed with your next dose immediately and continue at regular intervals as advised by your doctor. Do not take a double dose to make up for a forgotten dose.

Reconstitution and application

General instructions:

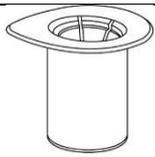
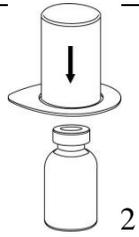
- The powder must be mixed (reconstituted) with the solvent (liquid) and withdrawn from the vial under aseptic conditions.
- The reconstituted solution should be clear or slightly opalescent, i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be checked by eye for small particles and discoloration, before it is administered. Do not use the solution if it is visibly cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

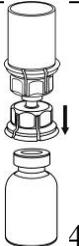
Reconstitution:

Without opening either vial, warm the Beriate powder and the solvent to room or body temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes.

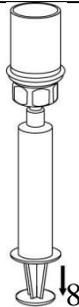
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37°C).

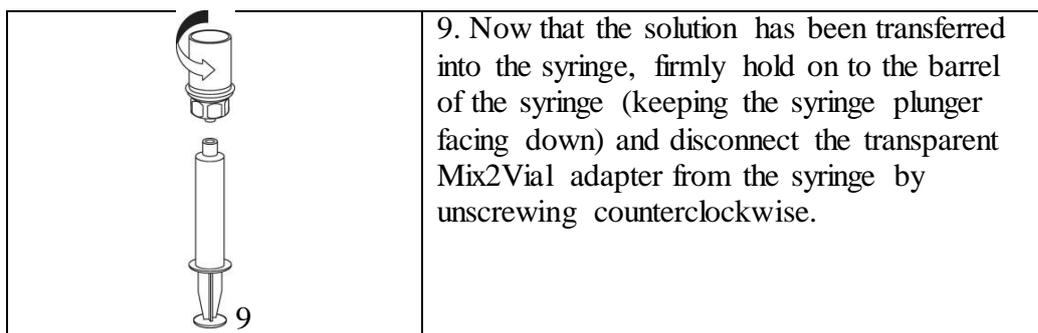
Carefully remove the protective caps from the vials containing powder and the solvent, and clean the exposed rubber stoppers with an alcohol swab. Allow the vials to dry before opening the Mix2Vial package, then follow the instructions given below.

 <p>1</p>	<p>1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!</p>
 <p>2</p>	<p>2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end straight down through the solvent vial stopper.</p>
 <p>3</p>	<p>3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling vertically upwards. Make sure that you only pull away the blister package, and not the Mix2Vial set.</p>

 <p>4</p>	<p>4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end straight down through the product vial stopper. The solvent will automatically flow into the product vial.</p>
 <p>5</p>	<p>5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.</p>
 <p>6</p>	<p>6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</p>
 <p>7</p>	<p>7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.</p>

Withdrawal and Application:

 <p>8</p>	<p>8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.</p>
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Use the venipuncture kit that is supplied with the product, insert the needle into a vein. Let blood flow back to the end of the tube. Attach the syringe to the threaded, locking end of the venipuncture kit. **Inject the reconstituted solution slowly into the vein** following the instructions given to you by your doctor. The injection or infusion rate should not exceed 2 ml per minute. Take care not to get any blood in the syringe containing the product.

Where a large volume is required, infusion is an alternative option. The reconstituted preparation should be transferred to an approved infusion system. Infusion should be carried out as instructed by your doctor.

Check yourself for any side effects that might happen straight away. If you have any side effects that might be related to the administration of Beriate, the injection or infusion should be stopped (see also section 2.).

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

4. Possible Side Effects

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

If any of the following happen, contact your doctor immediately or go to the Emergency Department or Haemophilia Centre at your nearest hospital:

- Symptoms of angioedema such as
 - swollen face, tongue or pharynx
 - difficulty to swallow
 - hives and difficulties to breath

These side effects have been observed very rarely (may affect up to 1 in 10,000 people), and may in some cases progress to severe allergic reactions (anaphylaxis) including shock.

- Loss of effect (continuous bleeding). You may very rarely develop an inhibitor (neutralising antibody) to Factor VIII, in which case Factor VIII will not work properly any more. If this happens, it is recommended that a specialised haemophilia centre be contacted.

Other side effects are:

- Allergic (hypersensitivity) reactions, which may include:
 - burning and stinging where the injection or infusion was given
 - chills, flushing, skin rash over the whole body, wheals

- headache,
- fall in blood pressure, restlessness, faster heart beat, tightness of the chest, wheezing
- tiredness (lethargy)
- nausea, vomiting
- tingling

These side effects have been observed very rarely, and may in some cases progress to severe allergic reactions (anaphylaxis) including shock.

- Very rarely, fever has been reported.

Side effects in children and adolescents

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V [to be completed nationally]. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Beriate

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

- Store in a refrigerator at 2°C to 8°C.
- Within the shelf-life, Beriate may be stored at up to 25°C, not to exceed a cumulative storage period of 1 month. The single room temperature periods should be documented in your treatment diary, to comply with the overall 1 month period.
- Beriate does not contain a preservative so the reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, a storage shall not exceed 8 hours at room temperature.
- Do not freeze.
- Keep the container in the outer carton in order to protect from light.
- **Keep out of the reach and sight of children.**

6. Contents of the pack and other information

What Beriate contains

The active substance is:

Beriate is presented as a powder (containing nominally 250 IU, 500 IU, 1000 IU or 2000 IU human coagulation Factor VIII per vial) plus a liquid (diluent). The reconstituted solution is for injection or infusion.

Beriate 250/500/1000 reconstituted with 2.5 ml, 5 ml and 10 ml respectively of water for injections contains approximately 100 IU/ml human coagulation Factor VIII. Beriate 2000 is to be reconstituted with 10 ml of water for injections and contains approximately 200 IU/ml human coagulation Factor VIII.

The other ingredients are :

Glycine, calcium chloride, sodium hydroxide (in small amounts) for pH adjustment, sucrose, sodium chloride. *Solvent:* Water for injection 2.5 ml, 5 ml and 10 ml respectively.

What Beriate looks like and contents of the pack

Beriate is presented as a white powder and is supplied with water for injection. The reconstituted solution should be clear to slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentations

Box with 250 IU containing:

- 1 vial with powder
- 1 vial with 2.5 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 5 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

Box with 500 IU containing:

- 1 vial with powder
- 1 vial with 5 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 5 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

Box with 1000 IU containing:

- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 10 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

Box with 2000 IU containing:

- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20

Administration set (inner box):

- 1 disposable 10 ml syringe
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

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

Austria:

Beriate 100 I.E./ml Pulver und Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung (250 I.E., 500 I.E., 1000 I.E.)
Beriate 200 I.E./ml Pulver und Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung (2000 I.E.)

Bulgaria:

Beriate 250 IU Powder and solvent for solution for injection or infusion
Beriate 500 IU Powder and solvent for solution for injection or infusion
Beriate 1000 IU Powder and solvent for solution for injection or infusion
Beriate 2000 IU Powder and solvent for solution for injection or infusion

Croatia:

Beriate 250 IU prašak i otapalo za otopinu za injekciju ili infuziju
Beriate 500 IU prašak i otapalo za otopinu za injekciju ili infuziju
Beriate 1000 IU prašak i otapalo za otopinu za injekciju ili infuziju
Beriate 2000 IU prašak i otapalo za otopinu za injekciju ili infuziju

Czech Republic:

Beriate 250 IU, Beriate 500 IU, Beriate 1000 IU, Beriate 2000 IU

Germany:

Beriate 250, Beriate 500, Beriate 1000, Beriate 2000

Hungary:

Presentations of Beriate 250, 500 and 1000:

BERIATE 100 NE/ml por és oldószer oldatos injekcióhoz vagy infúzióhoz

Presentation 2000:

BERIATE 200 NE/ml por és oldószer oldatos injekcióhoz vagy infúzióhoz

Italy:

Beriate

Poland:

Beriate

Portugal:

Beriate

Romania:

Beriate 250 pulbere și solvent pentru soluție injectabilă/perfuzabilă

Beriate 500 pulbere și solvent pentru soluție injectabilă/perfuzabilă

Beriate 1000 pulbere și solvent pentru soluție injectabilă/perfuzabilă

Beriate 2000 pulbere și solvent pentru soluție injectabilă/perfuzabilă

Spain:

Beriate 250 UI polvo y disolvente para solución inyectable o perfusión

Beriate 500 UI polvo y disolvente para solución inyectable o perfusión

Beriate 1000 UI polvo y disolvente para solución inyectable o perfusión

Beriate 2000 UI polvo y disolvente para solución inyectable o perfusión

Slovakia:

Beriate 250 IU

Beriate 500 IU

Beriate 1000 IU

Beriate 2000 IU

Slovenia:

Beriate 250 i.e. prašek in vehikel za raztopino za injiciranje/infundiranje

Beriate 500 i.e. prašek in vehikel za raztopino za injiciranje/infundiranje

Beriate 1000 i.e. prašek in vehikel za raztopino za injiciranje/infundiranje

Beriate 2000 i.e. prašek in vehikel za raztopino za injiciranje/infundiranje

This leaflet was last revised in May 2017

The following information is intended for medical or healthcare professionals only

Posology

Previously untreated patients

The safety and efficacy of Beriate in previously untreated patients have not yet been established. No data are available.

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

Patients should be monitored for the development of factor VIII inhibitors. See also section 2.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in IU (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment

The calculation of the required dosage of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by about 2 % (2 IU/dl) of normal activity. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired F VIII rise (% or IU/dl) x 0.5.

The amount to be administered and the frequency of the administration should always be oriented to the clinical effectiveness in the individual case.

In case of the following haemorrhagic events the factor VIII level should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours) / Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat infusion every 12-24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages:	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80-100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% - 60% (30-60 IU/dl corresponding to 0.30-0.60 IU/ml)

Prophylaxis

For long term prophylaxis against bleedings in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Paediatric population

Dosing in children is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case. Some experience from treatment of children less than 6 years exists.

Information on pharmacological properties of VWF

In addition to its role as a factor VIII protecting protein, von Willebrand mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.