EU SUMMARY OF PRODUCT CHARACTERISTICS – EU-SPC (EDS/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

SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally:
250/500/1000/2000 IU human coagulation factor VIII (FVIII).
After reconstitution with 2.5/5/10 ml Beriate 250/500/1000 contains 100 IU/ml factor VIII.
Beriate 2000 is to be reconstituted with 10 ml of water for injections and contains approximately 200 IU/ml factor VIII.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The mean specific activity of Beriate is approximately 400 IU/mg protein.

Produced from the plasma of human donors.

Excipient with known effect:
Sodium approximately 100 mmol/l (2.3 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion.
White powder and clear, colourless solvent for solution for injection/infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

This product may be used in the management of acquired factor VIII deficiency.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

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 4.4.

Posology:
The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

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 factor VIII rise [% or IU/dl] x 0.5.

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

In the case of the following haemorrhagic events, the factor VIII activity 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% (IU/dl).

Prophylaxis
For long term prophylaxis against bleeding 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 (see section 5.1).

Method of administration:
For intravenous use.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.
The preparation should be warmed to room or body temperature before administration. Inject or infuse slowly intravenously at a rate which the patient finds comfortable. The injection or infusion rate should not exceed 2 ml per minute.

Observe the patient for any immediate reaction. If any reaction takes place that might be related to the administration of Beriate, the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient (see also Section 4.4).

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

Hypersensitivity
Allergic type hypersensitivity reactions are possible. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of shock, the current medical standards for shock treatment should be observed.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for FVIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. The management of such

patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors. See also section 4.8 .

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

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

Appropriate vaccination (hepatitis A and hepatitis B) should be generally considered for patients in regular/ repeated receipt of human plasma-derived Factor VIII products.

It is strongly recommended that every time that Beriate is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Sodium content
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.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII.

Pregnancy and breastfeeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available.

Therefore, factor VIII should be used during pregnancy and breastfeeding only if clearly indicated.

Fertility
There are no data on fertility available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed very rarely, and may in some cases progress to severe anaphylaxis (including shock).

Patients with haemophilia A may very rarely develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The following adverse reactions are based on postmarketing experience as well as scientific literature.

The table presented below is according to the MedDRA system organ classification.

Frequencies have been evaluated according to the following convention: 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 (cannot be estimated from the available data).

MedDRA SOC	**Adverse Reaction**	**Frequency**
Blood and lymphatic system disorders	FVIII inhibition	Very rare
General disorders and administration site conditions	Fever	Very rare
Immune system disorders	Hypersensitivity (allergic	Very rare

	reactions)	

For information on viral safety see 4.4.

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

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 via the national reporting system listed in Appendix V [to be completed nationally].

4.9 Overdose

No symptoms of overdose with human coagulation factor VIII are known so far.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factors.
ATC code: B02BD02

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions.
When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation.

Activated factor VIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

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.

Data on treatment of 16 children less than 6 years of age are available and the clinical efficacy and safety results obtained were in line with the experience in older patients.

5.2 Pharmacokinetic properties

Following intravenous administration, factor VIII activity decreases mono- or biexponentially. The terminal half-life varies between 5 and 22 hours with a mean value of approximately 12 hours. The increase in factor VIII activity following administration of 1 IU factor VIII/kg bodyweight (incremental recovery) was approximately 2% with interindividual variability (1.5-3%). The mean residence time (MRT) was found to be 17 hours (standard deviation 5.5 hours), the mean area under the data completed by extrapolation (AUDC) was 0.4 h x kg/ml (standard deviation 0.2), the mean clearance 3 ml/h/kg (standard deviation 1.5 ml/h/kg).

Paediatric population
Limited pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

General toxicity:
Toxicological studies with repeated dosage have not been performed due to development of antibodies against heterologous protein.

Even doses of several times the recommended human dosage per kilogram body weight show no toxic effects on laboratory animals.

The tests of the heat-treated factor VIII preparation with polyclonal precipitating antibodies (rabbit) in the Ouchterlony assay and in the passive cutaneous anaphylaxis test in the guinea pig did not show changed immunological reactions, compared with untreated protein.

Mutagenicity:
Since clinical experience provides no hint for tumorigenic and mutagenic effects of human plasma coagulation factor VIII, experimental studies, particularly in heterologous species, are not considered meaningful.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Calcium chloride
Sodium hydroxide (in small amounts) for pH adjustment
Sucrose
Sodium chloride

Supplied solvent: Water for injections 2.5 ml, 5 ml and 10 ml respectively.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, solvents and diluents except those mentioned in section 6.1.

6.3 Shelf-life

3 years.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 8 hours at 25 °C. From a microbiological point of view the product should be used immediately. If it is not administered immediately, a storage shall not exceed 8 hours at room temperature.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.
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 to comply with the overall 1 month period.
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37ºC).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and content of container

Immediate Containers:
Injection vial of colourless glass (250 IU and 500 IU: Type I; 1000 and 2000 IU: Type II)), sealed under vacuum with rubber stopper (bromobutyl), aluminium cap and plastic disc (polypropylene).

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 20/20Administration set (inner box):- 1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

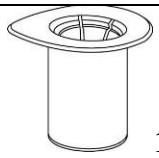
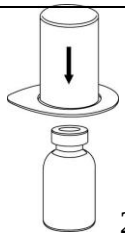
Not all pack sizes may be marketed.

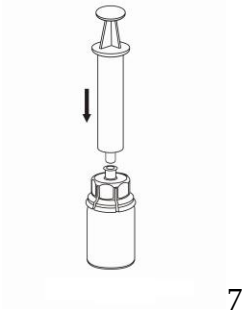
6.6 Special precautions for disposal and other handling

Method of administration

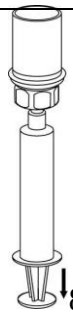
General instructions:
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or contain residues (deposits/particles).
- Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution:
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	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.
 3	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.
 4	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.
 5	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.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

 7	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.

Withdrawal and application:

 8	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.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

For injection of Beriate the use of plastic disposable syringes is recommended as the ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

Administer solution slowly intravenously (see section 4.2), taking care to ensure that no blood enters the syringe filled with product. 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.

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

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH

Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

- country-specific -

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- country-specific -

10. DATE OF REVISION OF THE TEXT

Date of last revision: May 2017