Public Assessment Report
for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Beriate

DE/W/0070/pdWS/001

Marketing Authorisation Holder:
CSL Behring GmbH

Rapporteur:	Germany (PEI)
Finalisation procedure (day 90):	30 June 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Beriate 250/500/1000/2000
INN (or common name) of the active substance(s):	human coagulation factor VIII
MAH:	CSL Behring GmbH
Currently approved Indication(s)	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). The product may be used in the management of acquired factor VIII deficiency.
Pharmaco-therapeutic group (ATC Code):	B02BD02
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection or infusion

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed due to submission of a final clinical study report.

II. RECOMMENDATION

Submission of new paediatric data of a final clinical study report do not change benefit-risk profile of Beriate and has therefore no impact on the SmPC. No consequential regulatory action is required.

III. INTRODUCTION

On 09.03.2016, the MAH submitted a completed clinical paediatric study for Beriate, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Beriate and that there is no consequential regulatory action.

The MAH proposed no changes to the product information.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

This paediatric worksharing procedure concerns a plasma derived Factor VIII that is indicated for the treatment and prophylaxis of bleeds in patients with haemophilia A.

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.

Beriate is provided as powder and solvent for solution for injection or infusion.

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 270 IU/mg protein.

According the current SmPC posology for paediatric population states as follows:

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.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for Study BI 81.021.2-5001 a prospective, open, uncontrolled, multicentre and observational study.

Title: Prospective pharmacovigilance using Beriate in haemophilia A patients.

2. Clinical study

Study BI 81.021.2-5001 Prospective pharmacovigilance using Beriate in haemophilia A patients.

- **Description**

To track routine treatment of haemophilia A patients who have been treated with Beriate for several years and to attain data on effectiveness, safety and tolerability of Beriate.

- **Methods**

Previously treated and untreated patients of any age with congenital F VIII deficiency were to be included in the surveillance. Once the investigator´s decision to enrol a patient was made, data collection for this patient started with the next treatment of Beriate.

Data on prophylactic, on-demand, and other treatment modalities during the surveillance were to be collected. At the first visit, basic patient data were recorded including information on individual haemophilia A disease. At all follow-up visits, bleeding episodes and their severity and inhibitor development were to be carefully documented. In addition, diseases and relevant conditions, concomitant medication and SADRs and routine medical care measurements were documented.

Patients for whom the treatment with Beriate was stopped were to be withdrawn from the surveillance.

- Objective(s)

Effectiveness:

- Reversal of coagulation factor deficit (increment in F VIII activity)
- Supporting clinical management of an acute bleeding episode.
- Incidence of spontaneously induced bleeding episodes.

Safety:

- Viral safety
- Incidence of inhibitor development.

Tolerability:

- Suspected adverse drug reactions (SADRs)

Pharmacoeconomics:

- Methodology

Previously treated and untreated patients of any age with congenital F VIII deficiencies were to be included in the surveillance.

Data on prophylactic, on-demand, and other treatment modalities during the surveillance were to be collected.

- Study population /Sample size

  Planned number of patients: a minimum of 150.

  Enrolled patients: 87.

  Age group < 6 years: 17

  Age group > 6 < 12 years: 10

  Age group ≥ 12 years: 60

  No subgroup analyses were performed.

  Main criteria for inclusion:

  Male or female patients of any age with haemophilia A (previously untreated and treated patients) receiving Beriate in accordance with Beriate prescribing information.

- Treatments

  Beriate, dose as required by the individual patient according to the nationally approved package leaflet.

- Statistical Methods

  Demographic data (age, sex, ethic group, body weight, height, and body mass index were analysed by means of descriptive summary statistics.

  Descriptive methods were also used for assessment of all effectiveness and safety variables.

  Between 2002 and 2014, informal interim analyses were performed on 5 separate occasions.

➢ **Results**

- Recruitment/ Number analysed

  Overall, 72 of 87 patients were documented as having received treatment with Beriate during the surveillance period. Of these 72, 56 patients received prophylactic treatment with Beriate at the last visit and 5 patients receiving Beriate treatment were untreated patients.

  A total of 12 (17.1%) patients were treated on-demand only.

  For 72 patients with available data, the median surveillance duration per patient was 465 days. The median number of infusions per bleed was 2.0.

- Efficacy results

  Clinical effectiveness was assessed in a total of 528 visits with available data during the surveillance period. For 98.7% of the visits documenting patients with minor bleeds, the effectiveness of the clinical response was rated as good or excellent.

- Safety results

  The incidence of SADRs was low, with only 4 patients at 4 (0.5%) visits documented as having SADRs during the surveillance (based on SADRs documentation at 888 visits overall). There were only two cases of F VIII inhibitor development during the surveillance: one patient, who has been previously treated with Beriate, developed a transient low-titre inhibitor that disappeared after an increase in his prophylactic dose. The second patient, a PUP, presented with a high-titre inhibitor and was treated with ITI. Due to lack of success of ITI the investigator switched the patient to bypass therapy.

  No thromboembolic events were reported and there was no proven virus transmission for hepatitis A, -B, -C or human immunodeficiency virus.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Main objective of study BI 81.021.2-5001 was the post-authorization surveillance of the safety and efficacy of Beriate and the discovery and reporting of adverse events, including potential thromboembolic events (TEEs) and potential viral transmission in patients of all age groups.

A demographic distribution of patients was listed in the clinical expert overview.

The applicant stated that the study results confirmed effectiveness, safety and tolerability of Beriate independent of the age. Effectiveness and safety results have not been discussed with special regard to children or adolescents.

Study results did not reveal any impact on the favourable benefit-risk profile of Beriate in patients of all age groups and therefore, no changes to the SmPC are recommended.

- **Recommendation**

Future submissions of paediatric worksharings according to Art. 46 data derived in paediatric population should be presented and discussed separately.

No further action required.

Comments that have been received from FR and NL support the rapporteur's assessment without further comments.