

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

**Haemate P**

**DE/W/0071/pdWS/001**

**Marketing Authorisation Holder:  
CSL Behring GmbH**

<b>Rapporteur:</b>	Germany (PEI)
<b>Finalisation procedure (day 120):</b>	17 November 2016

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Haemate P 250/500/1000
INN (or common name) of the active substance(s):	Human coagulation factor VIII and human von Willebrand factor
MAH:	CSL Behring GmbH
Currently approved Indication(s)	<p><b>Von Willebrand Disease (VWD)</b> Prophylaxis and treatment of haemorrhage or surgical bleeding, when desmopressin (DDA VP) treatment alone is ineffective or contra-indicated.</p> <p><b>Haemophilia A (congenital factor VIII deficiency)</b> Prophylaxis and treatment of bleeding in patients with haemophilia A. This product may be used in the management of acquired factor VIII deficiency and for treatment of patients with antibodies against factor VIII.</p>
Pharmaco-therapeutic group (ATC Code):	B02BD06
Pharmaceutical form(s) and strength(s):	Powder and solvent (water for injections) for solution for injection or infusion

## **I. EXECUTIVE SUMMARY**

No SmPC and PL changes are proposed.

## **II. RECOMMENDATION**

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

The company provided more detailed information with respect to the use of Haemate P in children as response to a request from RMS and NL.

## **III. INTRODUCTION**

On 09.03.2016, the MAH submitted a completed clinical paediatric study for Haemate P, 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 Haemate P and that there is no consequential regulatory action.

The MAH proposed no regulatory action.

## **IV. SCIENTIFIC DISCUSSION**

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

Haemate is a plasma derived F VIII/ von Willebrand factor (VWF) concentrate and is indicated in the treatment and prophylaxis of bleeds in patients with haemophilia A, VWD, acquired FVIII deficiency and treatment of haemophilia A patients with inhibitors. Haemate P is nationally licenced in Germany since 1982 and is licenced in more than 30 countries worldwide.

Haemate P is provided as freeze-dried powder and solvent for solution for injection and is licenced in three strengths:

Haemate P 250 IU

Haemate P 500 IU

Haemate P 1000 IU

A vial contains nominally:

250/500/1000 I.U. human coagulation factor VIII (FVIII) and

600/1200/2400 I.U. human von Willebrand Factor (VWF).

After reconstitution with 5/ 10 ml WFI Haemate P 250/500 contains 50 I.U./ ml FVIII and 120 I.U./ml VWF.

After reconstitution with 15 ml WFI Haemate P 1000 contains 66,6 I.U./ml FVIII and 160 I.U./ ml VWF.

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.

## **IV.2 Clinical aspects**

### **1. Introduction**

The MAH submitted a final report for Study BI8021\_5001 Prospective pharmacovigilance using Haemate P in von Willebrand disease patients or hemophilia A patients

### **2. Clinical study**

BI8021\_5001 Prospective pharmacovigilance using Haemate P in von Willebrand disease patients or hemophilia A patients.

#### **➤ Methods**

Previously treated and untreated patients with congenital VWF and/or FVIII deficiencies were to be included in the surveillance. Once the investigator's decision to enroll a patient was made, the data collection for this patient started with the next treatment of Haemate P. 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 VWD/hemophilia A disease. At all follow-up visits, bleeding episodes and surgeries including their severity and inhibitor development (in case of hemophilia A) were to be carefully documented. In addition, diseases and relevant conditions, concomitant medications and suspected adverse drug reactions (SADRs), and routine medical care measurements were documented. Patients for whom the treatment with Haemate P stopped were to be withdrawn from the surveillance.

- Objective(s)

The aim of this surveillance was to track routine treatment of VWD and hemophilia A patients who have been treated with Haemate P for several years and to attain data on the effectiveness, safety and tolerability of Haemate P. Study design.

- Study population /Sample size

Male or female patients of any age with VWD or hemophilia A who were previously treated or needed treatment with Haemate P in accordance with Haemate P prescribing information were included in this surveillance.

#### Demographic characteristics

		VWD				Hem A
					ALL*	
Sex						
Male	N (%)	20 (27.8)	14 (46.7)	3 (23.1)	37 (31.9)	14 (100.0)
Female	N (%)	52 (72.2)	16 (53.3)	10 (76.9)	79 (68.1)	–
Ethnicity						
Caucasian	N (%)	71 (98.6)	29 (96.7)	12 (92.3)	113 (97.4)	13 (92.9)
Oriental/Asian	N (%)	1 (1.4)	1 (3.3)	1 (7.7)	3 (2.6)	–
Other	N (%)	–	–	–	–	1 (7.1)
Age	Mean (SD)	34.7 (20.9)	34.2 (27.2)	25.2 (20.5)	33.5 (22.6)	9.4 (10.8)
Age group						
<6 years	N (%)	8 (11.1)	7 (23.3)	3 (23.1)	18 (15.5)	6 (42.9)
6 to <12 years	N (%)	3 (4.2)	4 (13.3)	–	7 (6.0)	5 (35.7)
≥12 years	N (%)	61 (84.7)	19 (63.3)	10 (76.9)	91 (78.4)	3 (21.4)
Weight (kg)	Mean (SD)	65.8 (25.9)	55.2 (27.9)	54.4 (25.0)	62.0 (26.5)	32.4 (19.8)
BMI (kg/m <sup>2</sup> )	Mean (SD)	24.1 (6.0)	23.2 (4.8)	23.1 (2.9)	23.8 (5.5)	18.4 (3.0)

Age, weight and BMI were documented at Visit 1 for all patients

BMI: body mass index; Hem A: hemophilia A; N: number of patients with available data; SD: standard deviation

VWD: von Willebrand disease

For patient 2204 the VWD Type was unknown.

- Treatments

The medication and dosage was to be based on the prescribing information included in the packaging. It was the responsibility of the investigator to follow the dosing instructions provided in the nationally approved package insert.

- Outcomes/endpoints

#### Effectiveness:

- Reversal of coagulation factor deficit (increment in VWF:RCo and FVIII activity)
- Supporting clinical management of bleeding episodes or surgery
- Incidence of bleeding episodes

#### Safety:

- Viral safety (where appropriate follow-up was to be guaranteed)
- Incidence of inhibitor development

#### Tolerability:

Suspected adverse drug reactions (SADRs) (e.g. allergic reactions) Statistical Methods

### ➤ **Results**

- Recruitment/ Number analysed

The surveillance study was conducted at 20 centers in Germany from 2000 to 2014. A total of 130 patients were enrolled: 116 patients had VWD and 14 patients had hemophilia A. The majority of VWD patients had VWD Type I (72 patients); 30 patients had VWD Type II and 13 patients had VWD Type III. For one patient, the VWD type was unknown.

Median duration of the surveillance was 2.2 months for VWD patients (range: 0 to 158.5 months) and 13.2 months for hemophilia A patients (range: 0 to 104.4 months)

- Efficacy results

The number of bleeds documented per year was similar in VWD and hemophilia A patients during the surveillance (median: 1.69 and 1.92 bleeds, respectively). Median number of infusions for all VWD patients was 1.0, whereby VWD Type I patients had a median of 4.0 infusions per bleed. Hemophilia A patients received a median number of 2.5 infusions per bleed.

The effectiveness of the clinical response was rated by the investigator as good or excellent in 92.9% of all 606 bleeds and 85.7% of all 84 surgeries documented during the surveillance.

- Safety results

The incidence of SADRs was low, with only 10 (1.7%) events being reported during the entire surveillance period (based on documentation of SADRs at 606 visits overall). There were no thromboembolic events reported. There was no proven virus transmission for hepatitis A-, hepatitis B-, hepatitis C- or human immunodeficiency virus (HIV).

### 3. Discussion on clinical aspects

The aim of this surveillance study was to collect and analyze data on the use of Haemate P in treatment of VWD and hemophilia A patients in routine medical practice.

A total of 130 patients were enrolled in the surveillance: 116 patients had VWD and 14 patients had hemophilia A. The majority of VWD patients had VWD Type I (72 patients); 30 patients had VWD Type II and 13 patients had VWD Type III. For one patient, the VWD type was unknown. The surveillance study took place from 2000 to 2014. Individual patient participation ranged from 0 to 158.5 months and median duration of participation in the surveillance was 1.6 months for VWD patients and 11.3 months for hemophilia A patients. In total, 14 (16.1%) patients were reported as withdrawn (9 [12.0%] of the VWD patients with available data and 5 [41.7%] of the hemophilia A patients with available data) from the surveillance. The most common reason for withdrawal was “lost to follow up”.

Of 129 patients with available data for exposure to treatment, 89 patients (76 VWD patients and 13 hemophilia A patients) received Haemate P on-demand or for prophylaxis during the surveillance; 19 patients receiving Haemate P were PUPs (17 VWD patients and 2 hemophilia A patients), and 24 patients (18 VWD patients and 6 hemophilia A patients) received prophylactic treatment at the last surveillance visit.

Median number of bleeds documented per year was similar in VWD and hemophilia A patients during the surveillance period (1.69 and 1.92 bleeds, respectively). The median number of infusions for all VWD patients was 1.0, whereby Type I VWD patients had a median of 4.0 infusions per bleed.

Hemophilia A patients received a median number of 2.5 infusions per bleed.

Clinical effectiveness was assessed for a total of 606 bleeding events and 84 surgeries for all 84 patients with available data during the surveillance period. In 92.9% of all bleeds and 85.7% of the surgeries, the effectiveness of the clinical response was rated as good or excellent.

The incidence of SADRs was low, with only 10 (1.7%) events being reported during the entire surveillance period (based on documentation of SADRs at 606 visits overall).

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

Taken together, the results confirmed the very good effectiveness, safety and tolerability of Haemate P in both VWD and hemophilia A patients.

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

Main objective of study BI8021\_5001 was the post-authorization surveillance of the safety and efficacy of Haemate P and the discovery and reporting of adverse events, including thromboembolic events (TEEs) and potential viral transmission in patients of all age groups.

Demographic distribution of patients was listed under point 11.1 of the final study report.

The applicant stated that the study results confirmed effectiveness, safety and tolerability of Haemate P independent of the age. Study results did not reveal any impact on the favourable benefit-risk profile of Haemate P in patients of all age groups and therefore, no changes to the SmPC are recommended.

### **➤ Recommendation**

Upon request, the MAH provided an amended clinical expert statement including a conclusion on paediatric population.

Comments that have been received from FR, NL, SE and the UK support the rapporteur's assessment.