Unit: Technical Assessment Unit

Public assessment report for biological products

Haemate 250IU-500IU

Administrative information:

Trade name of the medicinal product:	Haemate 250IU Haemate 500IU
INN (or common name) of the active substance(s):	Human Coagulation Factor VIII 250 IU / 600 IU Human von Willebrand Factor Human Coagulation Factor VIII 500 IU / 1200 IU Human von Willebrand Factor
Manufacturer of the finished product	CSL Behring GmbH Emil-von-Behring-StraBe 76 35041 Marburg - GERMANY;
Marketing Authorization holder	CSL Behring GmbH Emil-von-Behring-StraBe 76 35041 Marburg - GERMANY;
Applied Indication(s):	-**Von Willebrand disease (VWD)** Haemate P is used for the prevention and treatment of bleedings or surgical bleeding caused by the lack of von Willebrand factor. -**Hemophilia A** (congenital factor VIII deficiency), Haemate P is used to prevent or to stop bleedings caused by the lack of factor VIII in the blood. - It may also be used in the management of acquired factor VIII deficiency
Pharmaceutical form(s) and strength(s):	-Powder and solvent for solution for injection -Factor VIII 250 I.U.; Von Willebrand Factor (VWF) 600 I.U. Factor VIII 500 IU / Von Willebrand Factor (VWF) 1200 IU
Route of administration	I.V Injection/I. V infusion
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

AEs	Adverse events
aPTT	Activated Partial Thromboplastin Time
CV	Cardivascular
FDA	Food and Drug Administration
FVIII	coagulation factor VIII
FVIII:C	Factor VIII: Coagulant Activity
ITI	Immune Tolerance Induction
IU	International unit
IV	Intravenous
ICH	International Conference on Harmonization
kg	Kilogram
NOAEL	No adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
VWF	von Willebrand factor
VWF:RCo	von Willebrand factor ristocetin cofactor
VWD	von Willebrand disease

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

Haemate P is prepared from human plasma for fractionation and contains human plasma factor VIII and human von Willebrand factor in concentrated form and meets the requirements of the Ph. Eur. monograph "

Haemate P is licensed for the following therapeutic indications:

- Prophylaxis and treatment of bleedings in Hemophilia A (congenital factor VIII deficiency and acquired factor VIII deficiency
- Treatment of patients with antibodies against factor VIII
- Prophylaxis and treatment of bleedings in von Willebrand's disease

Haemate P is supplied in two different strengths with 250 IU or 500 IU of factor VIII activity (F VIII:C) and 600 IU or 1200 of VWF:RCo activity respectively.

1 mL of the reconstituted solution contains: - Haemate P 250 and 500: 50 IU F VIII:C and 120 IU VWF:RCo.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in aforementioned section

2.2.2 Drug Substance (Active ingredient)

- **General information**

European Pharmacopoeia name: Human Coagulation Factor VIII (plus Human von Willebrand Factor -

The active substance of Haemate P is a Factor VIII/von Willebrand factor complex isolated from human plasma. Factor VIII (FVIII) and von Willebrand factor (VWF) are two distinct plasma glycoproteins found associated as a noncovalent complex in plasma. plasma FVIII shows a heterogenous band pattern if analysed by SDS-PAGE and Western blot (theoretically bands between 80 kDa (light chain), 90-250 kDa (heavy chain) and 330 kDa

Mature VWF is a multimeric protein composed of covalently linked dimeric subunits of about 500 kDa. These dimers again contain two identical protein chains of 2050 amino acids each (about 255 kDa) covalently linked.The molecular weight of VWF multimers ranges from **500 kDa to about 20 000 kDa.**The complex formation of FVIII and VWF is mediated by the a3 region C2 domain of FVIII and D'/D3 domains of VWF. The drug substance is a sterile solution containing 40-60 IU/mL of factor VIII:C activity/mL. It is Colorless and clear to slightly opalescent solution

- **Manufacturer(s)**

The Active substance is manufactured at CSL Behring GmbH Emil-von-Behring-Str. 76

35041 Marburg Germany
The site complies with the GMP requirements

Description of Manufacturing Process and Process Controls.
Is manufactured from human plasma in a continuous manufacturing process. The drug substance of Haemate P is not isolated as intermediate. The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.
The manufacturing steps evaluated in the Haemate manufacturing process for virus reduction is provided.

Control of Materials.
The starting material human plasma for fractionation is in compliance with the requirements as described in the current Ph. Eur. Monograph Human Plasma for Fractionation (0853).
List of raw materials of Pharmacopoeial Standard with relevant COAs are provided.

Controls of Critical Steps and Intermediates.
Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart.

Process Validation
The process validations carried out confirmed that the Haemate P production process is well controlled and consistently and reproducibly delivers a drug product meeting its acceptance criteria and product quality attributes

Manufacturing Process Development.

The developmental history of the manufacturing process is sufficiently describing the whole changes made to the DS manufacturing process with proper justification. Detailed description for each step development is mentioned in the MA file.

Characterization.
During the life-cycle of Haemate P the consistency of the method of production has been evaluated and demonstrated by applying extensive analytical testing including the recommended procedures by the Ph. Eur. monography 0275. the results demonstrated the *biochemical equivalence* of the infusion-volume reduced Haemate P with normal human plasma and with the formerly licensed product.

Specification: The tests performed on the drug substance comply with the requirements of USP, Ph. Eur, and In-house practices.

Analytical Procedures.: analytical procedures with validation reports are provided in the CTD file.

Batch analysis: The results of drug substance compared to the data obtained from the consistency batches are provided in the CTD file and found to be satisfactory**.**

Reference Standards or Materials.:
the reference standard for the testing of the drug substance is provided. For routine testing, the standards are calibrated against the valid international reference standards.

Container closure system: The final bulk solution is stored in stainless steel tanks. The maximum holding time has been validated and Container Closure Integrity has been demonstrated in corresponding studies**.**

- **Stability of drug substance:** Based on available stability data
  - Approved Shelf Life: **18 Hours**
  - Approved Storage Conditions: **Store at room temperature (18-28 °C).**

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

-Haemate P is a powder and solvent for solution for injection or infusion. After reconstitution a clear to slightly opalescent solution.

- Pharmaceutical Development including brief description on Components of drug product. Haemate P DS is a sterile solution containing 40-60 IU/mL of factor VIII:C activity/mL and contains albumin (stabilizer), glycine (stabilizer), sodium chloride (electrolyte) and sodium citrate (electrolyte) as excipients. Compatibility between drug substance and the excipients has been demonstrated during development of infusion-volume reduced Haemate P and the routine manufacturing of its predecessors.

- Formulation Development
- Overages: filling volumes are checked by weighing to avoid unexpected overfill.

- Physicochemical and Biological Properties
The physicochemical and biological properties of Haemate P were investigated. Additional assays (multimer electrophoresis, collagen-binding assay and an additional Factor VIII activity test) were performed for more detailed elucidation of protein-chemical properties, product composition and functionality. These were found comparable in all tested lots and also in comparison with the non-infusion-volume reduced product.

- Manufacturing Process Development.

- Container closure system and their compatibility.
The container closure system adequately protects the dosage form, is compatible with the dosage form, is composed of materials that are considered safe for the use of the dosage form and route of administration and has confirmed sterility and stability by stability studies and container closure integrity.

- Microbiological Attributes.
Haemate P is sterile products which do not contain a microbial preservative and all **GMP principles are followed .** Sterility and endotoxin testing is performed in accordance with the requirements of the European Pharmacopoeia.

- Compatibility.
-The container/closure system was carefully selected to assure compatibility with the drug product. The container/closure system does not interact physically or chemically with the contents of Haemate P (infusion-volume reduced)

- **Manufacture of the drug product:**

The finished product is manufactured at CSL Behring GmbH Emil-von-Behring-Str. 76
35041 Marburg Germany
Manufacturing of DP is performed in accordance with cGMP regulations.

- **Description of manufacturing process and process controls along with manufacturers and responsibilities**.
- A flow diagram is clearly presented giving the steps of the process and showing where materials enter the process. The critical steps the process control parameters and points at which process control or final product controls are conducted are identified. A narrative description of the manufacturing process, including filling , lyophilization and packaging. are provided.

Control of critical steps and intermediates:
Production of Haemate P critical steps have been defined. Since the final bulk product represents the drug substance and the production process is a continuous process, no intermediates are defined.

- Process validation and / or evaluation.
The performed process validation included full-scale lyophilization validation, investigation of product holding times in the lyophilizes prior to the start of the lyophilization cycle, and media fills. In order to increase the total production capacity at the Marburg site and to assure full supply of its pharmaceuticals, CSL Behring GmbH has established an additional new filling and lyophilization area on the 4th floor in building M305.The validation study report are provided and results were satisfactory.

Product specification:

- Specifications and testing of the excipients are in accordance with the current European Pharmacopoeia.
- The specifications of the excipients comply with the requirements of the respective Ph. Eur. Monographs.
- The specifications for human albumin solution are provided in the CTD file which comply with the requirements of the Ph. Eur. monograph "Albumini Humani Solution".
- Human albumin solution is obtained from human plasma that meets the requirements of the Ph. Eur. monograph „Plasma humanum ad separationism".
- Excipients of animal origin are not used for the production of Haemate P.
- There are no novel excipients used.

Characterization of impurities.:
The levels of fibrinogen, haemagglutinins A and B, and aluminum as well as specific activity are routinely tested. In addition, the drug product is tested for sterility and endotoxins to detect microbial contaminants and bacterial endotoxins.

Batch analysis
Data are provided for each filling size (250/500 IU) in form of respective
Certificates of Analysis and all results comply with specification.

Reference Standards or Materials.: a list of reference standards for the testing of the drug product is provided. For routine testing, in-house standards are used, which are calibrated against the valid international reference standards**.**
Container closure system.: container closure system components comply with the requirements of the European Pharmacopoeia and the United States Pharmacopoeia.

- **Stability of the drug product.**

Approved shelf life for the Finished product:
Before opening: 3 years
After reconstitution: 3 hours at room temperature (max. +25 °C).
Approved Storage Conditions of the Finished product:
Before opening
Haemate P do not store above 25 °C.
Do not freeze.
Keep container in the outer carton, in order to protect from light.
After reconstitution: 3 hours at room temperature (max. +25 °C).

3. Non –clinical aspect:

➢ Haemate-P is in the pharmacotherapeutic group of antihemophilic, consists of two active ingredients (Highly purified human blood coagulation **FVIII** and **VWF**), which are purified from pooled human fresh-frozen plasma. Notably, the "P" in haemate-P stands for pasteurised. The ratio of Factor VIII to

VWF in Haemate-P is about 1:2.2. VWF acts as a natural or endogenous stabiliser for Factor VIII (one of the least stable of human therapeutic proteins). Haemate-P is designed to efficiently and safely substitute insufficient levels of functionally active FVIII and VWF. This product was granted **FDA** approval on 01/4/1999 under the trade name Humate-P.

- **Pharmacology:** Since the PD effect of haemate-P is demonstrated by its successful clinical use over several decades, no additional pharmacological studies were performed. Collectively, from the safety pharmacology studies with Haemate-P performed in a total of 11 dogs, it can be concluded that Haemate-P was well tolerated and an accumulated dose of **175 IU/kg** body weight caused no changes with toxicological significance of the CV and respiratory parameters recorded. NOAEL of Haemate-P was 175 IU/kg.

- **Pharmacokinetics:** The PK study demonstrated the bioequivalence of Haemate-P and Haemate-P infusion-volume reduced formulation. Previously conducted non-clinical studies with Haemate-P are consequently considered as valid for Haemate-P infusion-volume reduced formulation. The safety profile and the PDs of the product can therefore be regarded as not affected by the reduction of the infusion volume.

- Absence of pharmacology and other PK studies considered acceptable according to the nature of the product and ICH S6 R1, 2011 guideline.

- **Toxicology:** In single dose toxicity studies in mice, rats and rabbits, the product was well tolerated and did not cause adverse clinical effects and none of the animals died as a consequence of the treatment. For mice and rats, the tolerated accumulated dose was **200 IU/kg body weight** and was **100 IU/kg body** weight in rabbits. The studies performed to investigate the local tolerance and formation of neo-antigenic components by pasteurisation revealed no unwanted secondary effect of haemate-P.

- **Overall conclusion:** Haemate-P is well tolerated in preclinical studies at doses of a multiple of the clinical human dose and therefore the dose levels proposed for clinical use is considered safe. This conclusion is in full agreement with the long-term experience of this product in humans.

4. Clinical aspect:

Haemate-P (also known historically as Haemate-HS in Germany, Austria, and Switzerland until 2007) is a **plasma-derived von Willebrand factor (VWF) and factor VIII (FVIII) concentrate** indicated for the treatment of **hemophilia A**, **von Willebrand disease (VWD)**, and **immune tolerance induction (ITI)** in patients with FVIII inhibitors.

The clinical development program includes extensive data from **PK/PD studies**, **efficacy trials** in hemophilia A and VWD, and **ITI programs**, supported by robust post-marketing experience since 1981. Evidence demonstrates consistent correction of FVIII and VWF levels, normalization of bleeding time in VWD, effective perioperative hemostasis, and high response rates in ITI.

- **Clinical Efficacy and Immunogenicity**

1 Hemophilia A

Hemostatic efficacy:
In the key study (Prot. 008), **95%** of patients showed *good or moderate* efficacy; all surgical patients achieved *good* efficacy. Supportive studies confirmed expected hemostatic responses across bleeding and surgical settings.

Laboratory efficacy:
Significant **shortening of aPTT** post-infusion. **FVIII:C levels corrected** immediately with predictable recovery and accumulation with repeated dosing.

2 Von Willebrand Disease

Clinical efficacy:
Across key and supportive studies, **most ratings were 'excellent' or 'good'** for acute bleeding, surgical prophylaxis, and routine prophylaxis. Effective hemostasis was maintained for up to **14 days post-surgery**.

Bleeding time and laboratory markers:
Bleeding time was shortened or normalized in almost all patients. Strong increases in **VWF:RCo** and **FVIII:C** post-infusion, with predictable declines and repeat-dose recovery.

3 Immune Tolerance Induction (ITI)

In the OITI-RP program, **93% (13/14)** achieved complete success (inhibitor eradication, normalized recovery and half-life). Multiple published series (Kreuz, Scaraggi, Berntorp) show **~90% inhibitor elimination** with Haemate-P.
High FVIII inhibitor titers and treatment interruptions were associated with delayed or reduced success.
Haemate-P demonstrated lower in-vitro reactivity to FVIII inhibitors relative to several other concentrates.

- **Clinical Safety**

Safety data from **35 clinical studies** (12 key, 23 supportive), plus **post-marketing surveillance since 1981**.
Additional safety evidence from **6 ITI studies**.

Key safety findings:

- **No unexpected safety signals** associated with treatment for hemophilia A, VWD, or ITI.
- **Adverse events (AEs)** consistent with expectations for plasma-derived coagulation factors.
- No cases of viral transmission reported in the modern manufacturing era.
- FVIII neutralising antibodies (inhibitors) not induced in VWD patients.
- Thromboembolic events were rare and occurred mostly in the context of surgery or other risk factors.

- **Overall Conclusion**

- Haemate-P/Humate-P demonstrates:

- Predictable pharmacokinetic behavior for both FVIII and VWF constituents.
- Consistent clinical efficacy in achieving hemostasis in hemophilia A and VWD, including in surgical settings.
- Strong correction of bleeding time and laboratory coagulation parameters.
- Exceptional performance in immune tolerance induction, with high rates of inhibitor eradication.
- A favourable and well-characterised safety profile based on decades of clinical use.
- The totality of evidence supports Haemate-P/Humate-P as a reliable and effective VWF/FVIII replacement therapy.

➢ **Benefit–Risk Evaluation**

Benefits

- Effective in treating **bleeding episodes**, **surgical prophylaxis**, and **routine prophylaxis** in VWD and hemophilia A.
- Demonstrates **rapid correction of FVIII:C and VWF:RCo**.
- Proven **normalization of bleeding time** in VWD.
- High **success rate in ITI therapy**, including eradication of high-titer inhibitors.
- Long history of **global clinical use** with established efficacy.

Risks

- Typical risks associated with plasma-derived coagulation factors (e.g., infusion-related reactions).
- Potential for **FVIII inhibitor development in hemophilia A**, though lower when VWF-containing products are used. Minimal thromboembolic risk, primarily in high-risk perioperative settings.
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Benefit–Risk Conclusion

The **benefits substantially outweigh the risks**. Haemate-P provides reliable, predictable hemostatic control with a very long track record of safety and immunogenic stability. Its demonstrated effectiveness in ITI gives it a unique advantage over FVIII-only products.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.