25 April 2025
EMA/CHMP/125920/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation

Jivi

International non-proprietary name: Damoctocog alfa pegol

Procedure No. EMEA/H/C/004054/X/0033/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AS	Active substance
AST	Ammonium sulfate-treated
BHK	Baby hamster kidney cells
CCS	Container closure system
CHMP	Committee for Medicinal Products for Human Use
CPP	Critical process parameter
FP	Finished product
HMW	High molecular weight
HPLC-SEC	Size exclusion-high-performance liquid chromatography
ICH	International conference of harmonization
IPC	In-process controls
IU	International units
LC/HC	Light chain/high chain
LMW	Low molecular weight
NMT	Not more than
pdFVIII	Plasma-derived FVIII
PDE	Permitted Daily Exposure
PEG	Polyethylene glycol
PIP	Paediatric Investigation Plan
PFS	Diluent prefilled syringe
RP-HPLC	Reversed-phase high-performance liquid chromatography
SmPC	Summary of product characteristics
sWFI	Sterile water for injections
WFH	World Federation of Haemophilia

1. Background information on the procedure

1.1. Submission of the dossier

Bayer AG submitted on 12 September 2024 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variation(s) requested		Type
B.III.2.b	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	IA
B.II.b.2.a	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	IA

Extension application to add a new strength of Jivi 4000 UI powder and solvent for solution for injection for treatment and prophylaxis of bleeding in previously treated patients ≥ 7 years of age with haemophilia A (congenital factor VIII deficiency). Version 3.3 of the RMP has also been submitted.

In addition, the MAH has taken the opportunity to align the product information with the pre-specified language from the updated EC Excipient Guideline.

B.III.2.b - Change in the specifications of sterile water for injection to comply with an update of the relevant Ph. Eur. 11.1 monograph.

B.II.b.2.a - To replace manufacturing sites.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision PIP P/0195/2017, on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0195/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0195/2017.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised

orphan medicinal products.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	12 September 2024
The procedure started on	3 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 December 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 December 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 January 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	N/A
The MAH submitted the responses to the CHMP List of Outstanding Issues on	N/A
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	N/A
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jivi on	25 April 2025
The CHMP adopted a report on similarity of Jivi with Altuvoct and Roctavian on date (Appendix 2)	25 April 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Haemophilia A (congenital factor VIII [FVIII] deficiency) is a potentially life-threatening or seriously debilitating chronic disease. It is an inherited disease caused by mutations in the gene coding for FVIII which result in FVIII deficiency state.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Haemophilia A is clinically characterised by recurrent bleeding into tissue and joints leading to progressive joint destruction. The disease occurs worldwide with an estimated incidence of 1 to 2 in 10,000 births, affecting predominantly males.

2.1.3. Clinical presentation, diagnosis

Haemophilia A is usually diagnosed by measuring FVIII clotting activity (FVIII:C) level in the plasma of a patient. There is a direct correlation between FVIII activity levels and clinical manifestations. Haemophilia A is defined as severe if the plasma FVIII:C level (measured as IU/dL) is < 1%, moderate if it is between 1% and 5%, and mild if it is between > 5% and 40% of normal.

Haemophilia A can result in spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma. Bleeds occur in muscle, central nervous system, organs, soft tissue and most frequently in joints, which leads to joint damage and severe disability, with major effects on the physical, psychosocial, quality of life, and financial conditions of the haemophilia patients.

2.1.4. Management

Per the current recommendations of the WFH Guidelines for the Management of Haemophilia as well as of many national and international haemophilia organisations, the standard of care for all patients with severe haemophilia A is primary prophylaxis, defined as regular therapy with FVIII replacement products or other haemostasis products to prevent spontaneous bleeding. Primary prophylaxis should be initiated early in life prior to the onset of joint disease, before the second clinically evident joint bleed and before 3 years of age to prevent musculoskeletal complications from recurrent joint and muscle bleeds (Srivastava et al. 2020).

Hemlibra (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

Efanesoctocog alfa (Altuvoct) is a modified recombinant factor VIII that is designed to enhance the hemostatic function. It works by binding to activated factor X (Xa) to facilitate the conversion of prothrombin to thrombin, thereby promoting the clotting cascade effectively. Its unique structure allows for stable interaction with the coagulation system, improving its efficacy in controlling bleeding.

Both Hemlibra and Altuvoct can be used in all age groups.

Another treatment option is gene therapy of haemophilia A, Valoctocogene roxaparvovec (Roctavian), an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels. Roctavian is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Episodic or on-demand FVIII treatment, i.e., treating bleeds when they occur, is no longer considered the standard of care for the management of haemophilia as it does not alter the natural history of frequent and recurrent bleeding and related complications. Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days.

2.2. About the product

Jivi is a recombinant B-domain deleted human coagulation FVIII variant which is site specifically conjugated with a single maleimide-derivatized 60 kDa branched PEG (two 30 kDa PEG) at the cysteine 910 (amino acid 1840 in the full length FVIII sequence), resulting in a decreased clearance and extended half-life.

This application concerns an extension application to add a new strength of Jivi 4000 UI powder and solvent for solution for injection.

2.3. Type of Application and aspects on development

Not applicable.

2.4. Quality aspects

2.4.1. Introduction

The purpose of this line extension (LE) application is to introduce an additional dosage strength of 4000 IU for Jivi, to the already approved strengths of 250 IU, 500, 1000 IU, 2000 IU, and 3000 IU, powder and solvent for solution for injection.

The finished product is supplied as a lyophilized powder in a vial with sterile water for injections (WfI) contained in a pre-filled syringe (PFS) and a vial adapter to facilitate reconstitution and an intravenous administration set for convenience.

After reconstitution with the solvent (WfI) provided, one mL of solution of Jivi 4000 IU contains approximately 800 IU (4 000 IU/5 mL) of the active substance human coagulation factor VIII, damoctocog alfa pegol. Other ingredients are: histidine; sucrose; glycine (E 640), sodium chloride; calcium chloride dihydrate (E 509); polysorbate 80 (E 433); acetic acid, glacial (E260) for pH adjustment and water for injections (solvent).

The 4000 IU dosage strength in 5 mL fill size has the same nominal concentration as the currently licensed 2000 IU dosage strength in 2.5 mL fill size. The registered CMC information widely applies to the new proposed strength. The 3.2.S section of the currently approved dosage strengths applies to the proposed 4000 IU dosage strength.

2.4.2. Active Substance

The 3.2.S section of the currently approved dosage strengths applies to the proposed 4000 IU dosage strength. No changes have been made to the active substance part of the dossier.

2.4.2.1. General information

The International Non-proprietary Name (INN) of the active substance is damoctocog alfa pegol. Other non-proprietary names are "PEGylated B-domain deleted recombinant Factor VIII (PEG-BDD-rFVIII)" and "Antihemophilic Factor (Recombinant), PEGylated."

The active substance, damoctocog alfa pegol, is a site specifically PEGylated B-domain deleted recombinant human coagulation factor VIII, produced in baby hamster kidney cells (BHK), with a

60 kDa branched polyethylene-glycol (two 30 kDa PEG) moiety. The molecular weight of the protein is approximately 234 kDa.

2.4.3. Finished Medicinal Product

Description of the finished product

The dosage of 4000 IU/vial, like the approved dosages of 250, 500, 1000, 2000, 3000 IU/vial, is also presented in a glass vial, stoppered, and sealed with an aluminum seal and plastic flip top.

The finished product (FP) is supplied as a lyophilized powder in a vial for reconstitution with sterile water for injections contained in a prefilled syringe. After reconstitution with the solvent (WfI) provided, one mL of solution of Jivi 4000 IU contains approximately 800 IU (4 000 IU/5 mL) of the active substance human coagulation factor VIII, damoctocog alfa pegol.

Other ingredients are: histidine; sucrose; glycine (E 640), sodium chloride; calcium chloride dihydrate (E 509); polysorbate 80 (E 433); acetic acid, glacial (E260) for pH adjustment and water for injections (solvent). There are no novel excipients or excipients of human or animal origin.

The final sterile filtered bulk drug product produces the 4000 IU/vial dosage in a nominal fill size of 5 mL

The qualitative and quantitative composition of the 4000 IU/vial dosage along with the function and grade of the excipients used in preparation of the finished product have been presented.

The dossier has been updated to include adequate information on the composition of 4000 IU strength, 5 mL fill size.

Pharmaceutical development

Damoctocog alfa pegol lyophilisate is a PEGylated, B-domain-deleted recombinant Factor VIII product, designed for longer circulation half-life. The finished product is presented in six dosages (250, 500, 1000, 2000, 3000, 4000 IU/vial) using the same formulation excipient composition as Bayer's commercial rFVIII products. A fill size of 2.5 mL was developed for five damoctocog alfa pegol finished product dosages (250, 500, 1000, 2000, 3000 IU). In addition to the current licensed dosage strengths, a 4000 IU/vial with fill size of 5 mL was developed.

Formulation development studies for the 250 IU to 3000 IU reconstituted with 2.5 mL are leveraged to 4000 IU/vial dosage strength reconstituted with 5 mL. The 4000 IU/vial contains the same excipient composition as the formulations currently used for Bayer's commercially approved rFVIII products. Further, the 4000 IU/vial and 2000 IU/vial have the same nominal concentration (IU/mL) after reconstitution.

Overall, the extent of the pharmaceutical development is found adequate.

Physicochemical and biological properties

Originally, extended characterisation was carried out to investigate the physicochemical and biological properties of the damoctocog alfa pegol lyophilisate finished product.

The extended characterisation included a wide range of different methods and the primary, secondary and functional structure was confirmed, and different studies indicated consistent functional activity results for the damoctocog alfa pegol FP. The existing data presented for the physicochemical and biological properties of the finished product are considered applicable to the 4000 IU dosage and no new characterisation studies are performed. This is acceptable.

2.4.3.1. Manufacture of the product and process controls

Manufacturers

The manufacturers of the 4000 IU dosage strength are the same as the manufacturers for the currently approved dosage strengths (250/500/1000/2000/3000 IU).

All sites responsible for manufacture and control of the finished product operate in accordance with GMP.

The damoctocog alfa pegol FP manufacturing process is based on the platform process developed and validated for the currently marketed rFVIII products for the 250, 500, 1000, 2000, and 3000 IU dosage strengths.

Damoctocog alfa pegol FP manufacturing process involves thawing of the frozen active substance, dilution to appropriate target potency, sterile filtration, filling into vials, subsequent lyophilization, unloading, and packaging. The partially diluted bulk active substance for the 4000 IU/vial dosage is prepared similarly as the 250/500/1000/2000 IU dosage strengths and the sterile filtration and filling steps are identical, except for the final fill weight.

The flow diagram of the damoctocog alfa pegol lyophilisate bulking, and filling process for dosage 4000 IU with fill size 5 mL have been provided.

Controls of critical steps and intermediates

The applicant has defined critical process performance attributes (in-process controls) for the bulking and filling of dosage 4000 IU with fill size 5 mL.

The process performance attributes and the acceptance criteria are identical to the process performance attributes and the acceptance criteria for the approved 250/500/1000/2000/3000 IU dosage fill size 2.5 mL. The critical process parameters for the bulking and filling process are identical to the critical process parameters for the 250/500/1000/2000/3000 IU dosage fill size 2.5 mL. Except for the vial fill weight, the acceptance criteria for the critical process parameters are also identical.

The critical process parameters for the 5 mL fill size are identical to the critical process parameters for the 250/500/1000/2000/3000 IU dosage fill size 2.5 mL.

The critical process performance attributes (in-process controls) and critical process parameters are found adequate.

Process validation

The manufacturing process validation approach for the 4000 IU dosage strength (5 mL fill size) included challenge of the minimum and maximum target batch sizes. Several conformance batches were included. During process validation, the finished product manufacturing process parameters and in-process controls were evaluated. Each conformance batch was tested for compliance with the FP release specifications. Further, the uniformity and reproducibility of the freeze-drying process were evaluated. Overall, the validation approach is endorsed and the extent of the validation is found sufficient.

Bulk Formulation and Filling

The critical process parameters (CPPs) for the bulking, sterile filtration, and filling processes were monitored, and all CPPs were maintained within the specified ranges for all 4000 IU dosage strength conformance batches. Key process parameters were tracked for all conformance batches and were within the acceptance criteria. In-process performance attributes results were within the acceptance criteria.

Freeze-drying process

The CPPs for the freeze-drying processes were monitored, and all CPPs were maintained within the specified ranges for all 4000 IU dosage strength conformance batches. Key process parameters were tracked for all conformance batches and were within the acceptance criteria. Further, the batch release results showed that all conformance batches met the release acceptance criteria.

Conclusion

Based on the presented data, it is concluded the finished product manufacturing process for the 4000 IU dosage strength (5 mL fill size) is in a validated state, the manufacturing process of the 4000 IU dosage strength can be maintained within established parameters and consistently produces FP meeting in-process acceptance criteria and release specifications.

2.4.3.2. Product specification

The battery of tests listed on the finished product specification for release and stability is acceptable and in line with ICH Q6B. It includes control of identity, purity and impurities, potency and other general tests.

The release and shelf-life specifications for the 4000 IU strength (5.0 mL fill size) specifications include the same test parameters as for the currently approved 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU strengths. The release specification includes tests for identity, purity, potency, content, safety tests, test for excipients, and further test of physical and chemical parameters, which includes mandatory compendial requirements.

Stability indicating parameters are included in the shelf-life specification and an additional container closure system (CCS) integrity test is included as well. The test parameters on the shelf-life specification are identical to the approved specifications for the other strengths. The test parameters included in the release- and shelf-life specification are found appropriate.

The established specification; test parameters, acceptance criteria, and analytical procedures are based on regulatory requirements (ICH Q3B/Q6B, Ph. Eur.), alignment with Bayer's marketed products (Kogenate and Kovaltry), historical range, and/or statistical analysis of release and stability data where appropriate. The initial specification acceptance criteria, established based on Phase 3 clinical and conformance batches, have been re-evaluated based on statistical analysis of conformance batches and commercial batches (historical data). Specification acceptance criteria were determined based upon the allowed variation in related attributes, alignment with active substance specification acceptance criteria, and clinical experience. Further, specific activity specification acceptance criteria were previously adjusted to reflect an optimized method implemented for determination of rFVIII activity. Specification acceptance criteria for the post launch 4000 IU finished product dosage strength are aligned with that of the 2000 IU finished product on a per mL basis. This alignment is due to the 5 mL reconstitution volume of the 4000 IU in contrast to the 2.5 mL reconstitution volume of all other dosage strengths.

No elemental impurities above the calculated permitted daily exposure (PDE) for parenteral finished products were identified in line with ICH Q3D.

No nitrosating agent is used in the manufacturing process of the active substance and finished product. No nitrosamine is identified as a potential impurity from the active substance or finished product manufacturing process. Hence, the risk for presence of nitrosamines to be negligible. This statement is endorsed.

Overall, the approach for setting the specification acceptance criteria is endorsed and the proposed acceptance criteria for the 4000 IU strength is found appropriate, based on the data and justification provided.

Analytical procedures and validation of analytical procedures

The applied analytical procedures are in general identical to the analytical procedures for the approved strengths.

The reconstitution volume applied in the test for sterility is 5.0 mL as opposed to 2.5 mL for the approved strengths. The suitability of the damoctocog alfa pegol finished product for sterility testing for the 4000 IU FP has been confirmed.

The potency analytical procedure remains unchanged as no update required based on the introduction of the 4000 IU strength. The 4000 IU finished product reconstituted with 5.0 mL WFI has the same active ingredient and excipients as the 2000 IU finished product (2.5 mL reconstitution).

All analytical methods have been adequately described and considered validated.

Batch analysis

Batch information and test results for several commercial batches of damoctocog alfa pegol finished product 4000 IU dosage strength manufactured at commercial scale at the site have been provided.

All batches meet the specification acceptance criteria and confirm consistency of the manufacturing process.

Reference Standards

There are no changes to this section.

Container closure system

The proposed primary container closure system (CCS) for the 5 mL fill size, 4000 IU in a 10 mL colorless glass type I silica coated glass vial with bromobutyl grey type I stopper for lyophilization, is identical to the currently approved CCS.

There are no changes to this section.

2.4.3.3. Stability of the product

A shelf life of 2 years is claimed for the finished product when stored at 2 °C - 8 °C for the unopened vial.

The intended shelf-life for damoctocog alfa pegol finished product at 5 °C is 2 years from the date of manufacture. Within this period, damoctocog alfa pegol finished product may be stored for up to 6 months at a temperature up to 25 °C/60%RH. Therefore, the stability studies performed in line with ICH guidelines are divided into three real-time storage conditions from which the shelf-life for the damoctocog alfa pegol FP is projected and confirmed during the storage period.

Real-time, long-term stability evaluation consisted of storage at 5 °C through the shelf-life. An appropriate protocol for the real-time stability studies, including the three real-time storage conditions, has been provided. The accelerated and stressed stability studies have been concluded, and stability data and conclusion on these studies are provided.

Overall, the stability data provided (also leveraged from the existing strengths) supports the claimed shelf-life of 2 years for damoctocog alfa pegol finished product at 2 °C - 8 °C. The chemical and physical in-use stability after reconstitution has been demonstrated for 3 hours at room temperature. From a microbiological point of view the product should be used immediately after reconstitution. If not

used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.

Within its overall shelf life of 2 years, the product (when kept in its outer carton) may be stored at up to 25 °C for a limited period of 6-months. The end date of the 6 month storage period at a temperature up to 25 °C should be recorded on the product carton. This date should never exceed the expiry date printed on the outer carton. At the end of this period the product should not be put back in the refrigerator but should be used or discarded.

2.4.3.4. Adventitious agents

Jivi is produced without the addition of any human or animal derived protein in the cell culture process, purification, PEGylation or final formulation.

There were no changes to this section. Overall adventitious agents safety of Jivi is considered sufficiently assured.

2.4.4. Finished Medicinal Product – Diluent, 5 mL fill size

5.0 mL sterile water for injection is proposed as diluent for the damoctocog alfa pegol 4000 IU, 5.0 mL fill size. The MAH has applied for the authorisation of the use of pre-filled diluent syringes, with 5.0 mL sterile water for injections, from two different suppliers. These suppliers are approved for the diluent 2.5 mL sterile water for injections used for the approved strengths and configurations for damoctocog alfa pegol FP.

Flow diagrams and descriptions of the manufacturing of the WFI diluent were provided. All components comply with the requirements of Ph. Eur. Filling of the syringes with the filter-sterilised WFI is detailed for both manufacturers, including appropriate in-process controls. The diluent prefilled syringes are terminally sterilised in autoclaves, meeting the requirements of Ph. Eur. Storage is at 15°- 25°C.

The container closure components for the 5 mL fill volume are the same as those for both suppliers. The product-contact components of the syringe (5 mL fill volume) for reconstitution of Factor VIII (FVIII) include the 5 mL glass barrel, the plunger stopper, the lubricating silicone oil, and the tip cap. The non-product contact materials include the plunger rod.

The results of the testing showed that the plunger stopper and tip cap material are safe and suitable for the intended use as a container closure component for the 2.5 mL Diluent PFS. The plunger stopper and tip cap material are the same for both 2.5 mL and 5 mL.

The original compatibility studies were performed using damoctocog alfa pegol FP of 250 IU and 3000 IU dosages (2.5 mL fill size), with sterile water for injection (sWFI) from two types of prefilled diluent syringes (PFS), the vial adapter, and the administration sets planned for commercial application. Compatibility of the damoctocog alfa pegol FP with the vial adapter and administration devices was evaluated immediately after reconstitution, and after several hours at room temperature. All data met the acceptance criteria.

The results from the original compatibility studies demonstrate that the sWFI, and the vial adapter and the administration devices for commercial application are compatible with damoctocog alfa pegol FP. Based on this, it is accepted that no further compatibility studies are performed for the 5 mL sWFI.

Process validation included bulk WFI preparation and filtration, preparation and sterilisation/depyrogenation of components, filling of syringes and terminal sterilisation. All in-process

tests were within the acceptance ranges and microbiological testing confirmed the hold times prior to terminal sterilisation. This is acceptable.

The claimed shelf-life for the diluent is 48 months at 2 - 25 °C with no more than 6 months at 30°C. Based on the stability data, the shelf-life of 48 months at 2 - 25°C with no more than 6 months at 30°C for both suppliers of the PFS is considered acceptable.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

The finished product part of the dossier presented in support of the additional dosage strength of 4000 IU of Jivi, 5 mL fill size is of good quality.

The finished product is supplied as lyophilized powder in a stoppered glass vial with aluminum over-seal, with sterile water for injections contained in a prefilled syringe and a vial adapter to facilitate reconstitution and an intravenous administration set for convenience.

The manufactures of the 4000 IU dosage strength are the same as the manufactures for the currently approved dosage strengths (250/500/1000/2000/3000 IU).

The damoctocog alfa pegol FP manufacturing process is standard and consists of thawing of the frozen active substance, dilution to appropriate target potency, sterile filtration, filling into vials, subsequent lyophilization, unloading, and packaging. The FP manufacturing process description is adequate and acceptable. The submitted manufacturing process validation data document that FP manufacturing process for the 4000 IU dosage strength (5 mL fill size) is in a validated state, the manufacturing process of the 4000 IU dosage strength can be maintained within established parameters and consistently produces FP meeting in-process acceptance criteria and release specifications.

5.0 mL sterile water for injection is proposed as diluent for the damoctocog alfa pegol 4000 IU, 5.0 mL fill size. The MAH has applied for the authorisation of the use of prefilled diluent syringes, with 5.0 mL sterile water for injection, from two different suppliers. These suppliers are approved for the diluent 2.5 mL sterile water for injections used for the approved strengths and configurations for damoctocog alfa pegol FP.

A finished product shelf life of 2 years at 2-8°C is supported by the stability data presented.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Jivi is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, this line extension application for Jivi to introduce and additional dosage strength of 4000 IU is considered approvable from the quality point of view.

2.4.7. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by

the CHMP.

2.5.1. Ecotoxicity/environmental risk assessment

Jivi is a recombinant replacement protein of the naturally occurring coagulation factor VIII. It is catabolised during human metabolism and no active molecule is excreted by the patient. In accordance with the guideline CHMP/SWP/4447/00 (1), Jivi as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment. Discussion on non-clinical aspects

No new non-clinical data have been submitted by the MAH. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, damactocog alpha pegol is not expected to pose a risk to the environment.

2.5.2. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted to support this application.

2.6. Clinical aspects

No new clinical data have been submitted in this application.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 1 Summary of safety concerns

Important identified risks	• Development of FVIII inhibitors • Hypersensitivity reactions • Loss of efficacy associated with anti-PEG antibodies
Important potential risks	• Off-label use • Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs • Thromboembolic events
Missing information	• Use in patients with severe hepatic impairment • Use in patients with renal insufficiency • Use in elderly patients >65 years of age • Safety profile in women including pregnancy and lactation

PEG: Polyethylene Glycol

2.7.2. Pharmacovigilance plan

Table 2 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Prospective multinational non-interventional Post-Authorisation Safety Study (PASS) study 20904 HA-SAFE	To provide long-term safety data to investigate safety risks associated with Jivi use for prophylaxis in the real-world settings, including the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs, hypersensitivity reactions, loss of efficacy, development of FVIII inhibitors	Potential long-term PEG-related adverse reaction (ARs) Hypersensitivity reactions Loss of efficacy associated with anti-PEG antibodies Development of FVIII inhibitors	First Patient Visit Study completion Study Report	Q2 2021 Q2/2028 Q4/2028
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
EUHASS (EUropean HAemophilia Safety Surveillance) registry (study 14149)	The EUHASS registry is an investigator-driven registry that is funded by the European Union (EU) in addition to Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective Haemophilia Safety Surveillance System for Europe. Participating centres have agreed to report all relevant AEs in their patients in a prospective manner. Events, that should be reported, are: new inhibitors, infections, allergic reactions, thromboses, new malignancies, and deaths.	Development of FVIII inhibitors Hypersensitivity reactions Potential long-term PEG-related ARs Use in patients with renal insufficiency Use in patients with hepatic impairment	Enrolment of first patient receiving Jivi Quarterly listings Annual report End of data collection Reporting of study results	Q4 2018 – Q1 2019 One quarter following the end of the reporting period (Upon receipt from EUHASS) Received by MAH 1 year after the end of the reporting period (Upon receipt from EUHASS); Submitted as part of the PSUR. 2027 PSUR based on annual reports from the registry

AR: Adverse Reaction; EU: European Union; EUHASS: EUropean HAemophilia Safety Surveillance; MAH: Marketing Authorization Holder No: Number; PBRER: Periodic Benefit-risk Evaluation Report; PEG: Polyethylene Glycol; PSUR: Periodic Safety Update Report; SN: Study Number

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 3.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the proposed new strength has been integrated into this already established package leaflet. The layout of the leaflet will remain unchanged.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Jivi is indicated for treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency). Restriction of the indication was due to safety concerns regarding potential effects of long-term PEG exposure. To support the proposed paediatric extension of the indication, the MAH provided the integrated analysis of Alfa-PROTECT Part A and the PROTECT Kids main study which included data from patients aged 7 to <12 years, focusing on the incidence of immune response to PEG within the first 4 exposure days and its impact on treatment efficacy.

3.1.1. Disease or condition

Haemophilia A (congenital factor VIII [FVIII] deficiency) is a potentially life-threatening or seriously debilitating chronic disease. It is an inherited disease caused by mutations in the gene coding for FVIII which result in FVIII deficiency state.

3.1.2. Available therapies and unmet medical need

Per the current recommendations of the WFH Guidelines for the Management of Haemophilia as well as of many national and international haemophilia organisations, the standard of care for all patients with severe haemophilia A is primary prophylaxis, defined as regular therapy with FVIII replacement products or other haemostasis products to prevent spontaneous bleeding. Primary prophylaxis should be initiated early in life prior to the onset of joint disease, before the second clinically evident joint bleed and before 3 years of age to prevent musculoskeletal complications from recurrent joint and muscle bleeds (Srivastava et al. 2020).

Hemlibra (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

Efanesoctocog alfa (Altuvoct) is a modified recombinant factor VIII that is designed to enhance the hemostatic function. It works by binding to activated factor X (Xa) to facilitate the conversion of prothrombin to thrombin, thereby promoting the clotting cascade effectively. Its unique structure allows for stable interaction with the coagulation system, improving its efficacy in controlling bleeding.

Both Hemlibra and Altuvoct can be used in all age groups.

Another treatment option is gene therapy of haemophilia A, Valoctocogene roxaparvovec (Roctavian), an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels. Roctavian is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Episodic or on-demand FVIII treatment, i.e., treating bleeds when they occur, is no longer considered the standard of care for the management of haemophilia as it does not alter the natural history of frequent and recurrent bleeding and related complications. Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days.

The MAH has applied extension application to add a new strength of Jivi 4000 UI powder and solvent for solution.

3.2. Conclusions

The overall benefit/risk balance of Jivi for the applied extension application to add a new strength of Jivi 4000 UI powder and solvent for solution is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Jivi is not similar to Altuvoct and Roctavian within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the benefit-risk balance of Jivi new strength is favourable on the following indication:

On 25 April, the CHMP recommended a positive opinion for the following extension of indication: Treatment and prophylaxis of bleeding in previously treated patients ⩾ 7 years of age with haemophilia A (congenital factor VIII deficiency).

The CHMP therefore recommends the extension of the marketing authorisation for Jivi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post Authorisation Safety Study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a non-interventional post-authorisation safety study according to an agreed protocol.	Study ongoing. Final study report should be submitted by 31 December 2028

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0195/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.