18 October 2018
EMA/CHMP/799360/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vihuma

International non-proprietary name: simoctocog alfa

Procedure No. EMEA/H/C/004459/X/0006/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

CSR	Clinical study report
EPAR	European Public Assessment Report
FVIII	Factor VIII
FVIII:C	Factor VIII activity
Human-cl rhFVIII	Human cell line recombinant human factor VIII
IS	International standard
IU	International unit
rFVIII	Recombinant human coagulation factor VIII
PTP	Previously treated patients
PUP	Previously untreated patients

1. Background information on the procedure

1.1. Submission of the dossier

Octapharma AB submitted on 30 May 2018 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.1.b	C.I.1.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union referral procedure - The product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	IB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	II

Extension application to add new strengths of 2500 IU, 3000 IU and 4000 IU, powder and solvent for solution for injection.

The above line extension is grouped with the following variations:
- C.I.4 - to update sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from Previously Untreated Patients (PUP) from GENA-05 (interim report) study
- C.I.11.b - to update the Risk Management Plan (version 10) to align the content in a single harmonised worldwide version for simocotocg alfa (rFVIII).
- C.I.1.b - to update the Product Information with the wording agreed in the Art. 31 referral (EMEA/H/A-31/1448).

The legal basis for this application refers to:

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

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	30 May 2018
The procedure started on	21 June 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 September 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 September 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 October 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension and group of variations to the granting a marketing authorisation of Vihuma on	18 October 2018

2. Scientific discussion

2.1. Problem statement

The MAH has submitted a grouping application for Vihuma (EU/1/16/1168/001-004) including an extension application, two Type II variations and one Type IB variation. The MAH wants to align the dossier and the product information of Vihuma to the dossier and product information of Nuwiq (EU/1/14/936/001-007), which is the reference product of Vihuma.

The following changes are included in this grouped extension application of Vihuma X/06/G:

1) Extension application - Item 1:
   → reference is made to NUWIQ/X/20

Introduction of new product strengths: 2500 IU, 3000 IU and 4000 IU

2) Type II Variation (Type II, C.I.4) - Item 2:
   →reference is made to NUWIQ/II/17/G

Update of the Product Information (sections 4.2, 4.8 and 5.1) and of the RMP (version 10) with data from Previously Untreated Patients (PUP) from GENA-05 (interim study report).The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Product Information throughout to bring it in line with the Core summary of product characteristics for human plasma-derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev. 2) and with the QRD version 10 (affects labelling only).

3) Type II Variation (Type II, C.I.11) - Item 3:
→Reference is made to NUWIQ/II/17/G

Submission of an updated Risk Management Plan (version 10) to align the content in a single harmonised worldwide version for simocotocg alfa (rFVIII)

4) Type IB Variation (Type IB, C.I.1b) - Item 4:
→ reference is made to Art. 31 Referral (EMEA/H/A-31/1448)

Update of Product Information to implement the wording agreed in the Article 31 referral (EMEA/H/A-31/1448). At time of initiation of the referral, Vihuma was not approved and thus was not within the scope of the referral.

2.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterized by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

2.1.2. Epidemiology

The overall reported number of haemophilia A patients estimated in the 2013 survey by the World Federation of Haemophilia (WFH) included 107 countries with a total population of 6,461,067,861 and identified 140,313 people with haemophilia A (2.2 per 100,000 individuals). There are currently approximately 30,000 patients in the EU with a mean prevalence of approximately 0.6 patients per 10,000.

Haemophilia A is inherited as an X-linked recessive trait and the main risk factors are therefore family history and a carrier mother. Approximately 30% of patients have no family history of the disease; their disease is presumably caused by new mutations.

2.1.3. Biologic features

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.

2.1.4. Clinical presentation, diagnosis

Haemophilia A manifests as profuse bleeding into the joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function (Bolton-Maggs and Pasi, 2003). The majority of bleeding occurs internally into joints, most commonly hinged joints such as the ankles, knees, and elbows. Serious bleeds also occur in muscles, especially in deep compartments such as the iliopsoas, calf and forearm, and in the mucous membranes in the mouth, gums, nose, and genitourinary tract. Less frequently, life threatening bleeds can occur in or around vital areas or organs such as the gastrointestinal system or enclosed areas like the intracranial or intracerebral spaces. The approximate frequencies of bleeds at the different sites are: 70 to 80% in joints (haemarthrosis), 10 to 20% in muscle, 5 to 10% in the central nervous system, and < 5% for bleeds at all other sites (Srivastava et al., 2013).

2.1.5. Management

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a “close to normal” life.

About the product

Vihuma is a duplicate of NUWIQ which was authorised via centralised procedure on 22. July 2014.

Vihuma 250 IU/500 IU/1000 IU/2000 IU were approved in Europe via informed consent application on 13.February 2017.

The active substance of Vihuma is simoctocog alfa (human coagulation factor VIII). Vihuma is produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) 293F cells.

Vihuma is a white sterile lyophilized powder and solvent for solution for injection. The lyophilized powder is supplied in single-dose vials containing 250 IU, 500 IU, 1000 IU, 2000 IU (2500 IU, 3000 IU or 4000 IU) of recombinant factor VIII per vial. Before use, the lyophilized powder is reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterilised water for injections. The reconstituted solution is a clear, colourless solution, practically free from visible particles, containing 100 IU / 200 IU / 400 IU / 800 IU (1000 IU / 1200 IU / 1600 IU) FVIII:C/mL.

Type of Application and aspects on development

The extension application is based on quality data and on non-clinical local tolerance data.

The non-clinical data package comprising of pharmacology, pharmacokinetics and toxicology data has been assessed in the course of the marketing authorisation procedure and is still applicable for the current extension procedure.

Therefore, only new local tolerance study of four Vihuma strengths following a single perivenous administration in rabbits was performed as part of this application.

2.2. Quality aspects

2.2.1. Introduction

Vihuma is a duplicate of Nuwiq. With this submission, it is intended to align the Vihuma marketing authorisation with the marketing authorisation for Nuwiq, as currently approved. The changes included in this line extension application are identical to those implemented for Nuwiq (EMEA/H/C/2813/X/20). The SmPC, labelling and package leaflet of Vihuma is fully aligned with Nuwiq.

Vihuma is supplied as a lyophilised powder and solvent for solution for injection. The lyophilised powder is currently available in single-dose vials containing 250 IU, 500 IU, 1000 IU and 2000 IU of recombinant factor VIII and is reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterile water for injections (WfI). With this line extension application the marketing authorisation holder is introducing single-dose vials containing the following new strengths: 2500 IU, 3000 IU and 4000 IU which are also reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterile water for injections.

2.2.2. Active Substance

The active substance of Vihuma is simoctocog alfa, a B-domain deleted human coagulation factor VIII produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) 293F cells (human cell line rhFVIII).

The cell line has been adapted to grow in a defined medium free from animal derived compounds. The harvested product is concentrated and purified by a series of chromatography steps, which also include solvent/detergent (S/D) treatment for virus inactivation/removal. Moreover, the reduced molecular size of the B-domain deleted rFVIII molecule allowed the introduction of nanofiltration as a second virus reduction step within the active substance purification process. No animal or human derived materials are added during the manufacturing process or to the final medicinal product.

Compared to the currently licensed strengths (250 IU, 500 IU, 100 IU and 2000 IU), the intended higher strengths of 2500 IU, 3000 IU and 4000 IU are manufactured identically up to and including the active substance (AS) level. There are no changes to the manufacture of the active substance. Changes to the 3.2.S. section of the dossier are related to some analytical methods which needed adaptation of e.g. dilutions due to the higher BDD-rFVIII concentrations and to the section *Characterisation* (3.2.S.3) in which results of comparability studies with respect to biological activity, physico-chemical characteristics as well as the impurity profile have been provided. These studies are presented and discussed in the finished product section below.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Vihuma finished product is a white sterile lyophilised powder and solvent for solution for injection. The lyophilised powder is supplied in single-dose vials containing 250 IU, 500 IU, 1000 IU, 2000 IU, 2500 IU, 3000 IU and 4000 IU of recombinant factor VIII per vial. The finished product is formulated with sodium chloride, sucrose, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188. Before use, the lyophilised powder is reconstituted with a single-dose solvent pre-filled syringe containing 2.5 mL of sterilised water for injections. The reconstituted solution is a clear, colourless solution, practically free from visible particles containing 100 IU / 200 IU / 400 IU / 800 IU / 1000 IU / 1200 IU / 1600 IU FVIII:C/mL. The concentration of each of the excipients is the same for all strengths, only the recombinant FVIII concentration varies. All excipients are of Ph. Eur. quality.

Pharmaceutical Development

Commercial production of Vihuma active substance was initially performed and validated in a bioreactor scale production line. Commercial Vihuma finished product is produced at the pharmaceutical production line. The production process of Vihuma was presented within the initial marketing authorisation application (MAA).

Subsequently, the production process of Vihuma has been scaled up, “Bio1”, with resulting larger scale purification to active substance (AS) and commercial pharmaceutical production of finished product (FP) in a new pharmaceutical line for filling of small volume parenterals (SVP) hereafter referred to as “Bio1 DP (SVP)”.

This line extension applies for the addition of the new product strengths of 2500 IU, 3000 IU and 4000 IU in addition to the currently approved product strengths 250 IU, 500 IU, 1000 IU, 2000 IU. Concerning the line extension, a Process validation (PV) has been performed for these new Vihuma strengths in Bio1 DP SVP.

In relation to pharmaceutical development compatibility of Vihuma finished product new strengths with the components used for reconstitution and injection of the product, including the 2.5 mL sterilized water for injections in a prefilled syringe was shown in study OC16-0517 and revealed no concerns regarding compatibility of Vihuma new strengths with reconstitution and injection devices.

Manufacture of the product and process controls

The manufacturing process of Vihuma finished product Bio1 DP SVP is identical compared to the approved manufacturing process. The “Method of Preparation” was updated with strength-specific details to include

the new product strengths of 2500 IU, 3000 IU and 4000 IU. The in-process controls and the control of critical steps have not been affected.

One batch of finished product is defined as containing 250 IU, 500 IU, 1000 IU, 2000 IU, 2500 IU, 3000 IU or 4000 IU Vihuma per vial, corresponding to approximately 1-36 Mio IU Factor VIII.

Process validation

Process validation was performed for the pharmaceutical production of Vihuma new product strengths from thawing and pooling of active substance to final container finished product in the SVP production line.

Process validation included five finished product batches using a bracketing approach covering all three strengths, minimum and maximum batch sizes and all identical freeze-dryers. Maximum hold times were challenged for one batch of each strength. Process control parameters and quality attributes determined at each manufacturing step were within acceptance criteria and comparable to ranges observed for Bio1 process validation batches of Vihuma 250, 500, 1000 and 2000 IU.

Product specification

Specifications of Vihuma finished product are unchanged except the strength-specific parameter potency and total protein.

Due to the new strengths and higher protein concentrations the test methods electrophoretic examination, factor VIII chromogenic test and molecular size distribution and the validations for endotoxin, sterility and molecular size distribution were adequately updated.

Batch release testing results confirmed the consistent manufacture of batches of the new strengths within specifications.

Stability of the product

Stability data for 5 batches Vihuma (1x 2500 IU/vial, 1x 3000 IU/vial and 3x 4000 IU/vial) as well as 12 months for 1 batch (1x 4000 IU/vial) for storage at 5°C have been provided in compliance with ICH Q5C. Stability at 25°C is completed for all 5 batches. Three batches, one of each strength, were also stored at 30°C for 6 months. Reconstitution studies were performed on one batch of the respective strength 2500 IU, 3000 IU and 4000 IU and covered 12 months storage at 5°C followed by reconstitution and storage at 25°C up to 24 hours.

Photo stability studies indicated a slight loss in FVIII potency and specific activity, when stored under light, requiring storage of the vials protected from light. A respective statement is included in the product information.

Parameters tested are appearance, visual inspection of solution, solubility, pH value, FVIII:C, total protein, specific FVIII:C activity, retention times and molecular size distribution by size-exclusion high performance liquid chromatography (SEC-HPLC), electrophoretic examination by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), osmolality, water content, integrity testing by head space analysis, sterility, endotoxin, particulate matter and concentrations of citrate, sucrose, poloxamer 188, sodium, calcium, chloride and arginine.

The results generated during the stability studies support the proposed shelf life of 24 months at 2°C – 8°C. During the shelf life, the product can be kept at room temperature (up to 25°C) for a single period

not exceeding 1 month. Once the product has been taken out of the refrigerator it must not be returned to the refrigerator. Within the proposed shelf life the finished product is stable up to 24 hours after reconstitution when stored at room temperature. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Comparability exercise for Finished Medicinal Drug Product

Compared to the currently licensed strengths (250 IU, 500 IU, 100 IU and 2000 IU), the intended higher strengths of 2500 IU to 4000 IU are manufactured identically up to and including the active substance level.

The higher strength vials require the processing of higher Vihuma concentrations during finished product manufacturing. As this process change may affect the biological activity profile of Vihuma downstream of the change, the biological activity of the 2500-4000 IU/vial process validation finished product batches were analysed in parallel to reference batches from both the original bioreactor and Bio1 DP. For the 2500-4000 IU/vial process validation batches, all earlier process steps up to and including AS were already characterised previously (230CBA139/BIO1/01).

The process validation for higher strength Vihuma comprised two independent campaigns resulting in six FP batches, with one 2500 IU/vial batch, one 3000 IU/vial batch, and four 4000 IU/vial batches.

To demonstrate comparability between the new product strengths and current product strengths, comparability with respect to biological activity, physicochemical characterisation as well as impurity profile was addressed.

Biological activity

For evaluation of comparability with respect to biological activity the following methods were applied:

- FVIII activity (chromogenic assay, Coatest SP FVIII kit)
- Specific activity
- FVIII activity/FVIII:Antigen ratio (Asserachrom VIII:Ag kit)
- Thrombin generation
- FXa generation
- Interaction with Activated Protein C
- vWF binding

Based on the provided data for 6 batches of the new strengths and the data for 8 batches of the already licensed strengths, the new strengths showed comparable characteristics in all assays.

Physico-chemical characterisation

Physico-chemical characterisation included SDS-PAGE under reducing and non-reducing conditions with silver staining, protein chip capillary electrophoresis, intrinsic fluorescence, asymetrical flow field-flow fractionation and HPLC gel filtration. The data support comparability between the currently approved and the new Vihuma strengths regarding these parameters.

Process related impurities

Analysis for impurities included testing for endotoxins, sterility, host cell protein (HCP) as well as aggregates and degradation products. The data support comparability between the currently approved and the new Vihuma strengths regarding the impurity profile.

In conclusion, comparability data provided for the addition of the 3 higher Vihuma strengths showed comparability with the currently licensed strengths.

Adventitious agents

The virus and TSE safety of human-cl rhFVIII has been sufficiently demonstrated. Human-cl rhFVIII is considered safe with respect to a potential transmission of TSE and viruses. There were no changes to the currently approved MAA for Vihuma.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension application concerns the addition of three new strengths for Vihuma (2500 IU, 3000 IU and 4000 IU). There are no changes to the manufacture of the active substance.

The new strengths differ only in the amount of active substance per vial. All the other excipients have the same concentrations. The solvent for reconstitution (WfI) as well as the primary packaging are also unchanged.

Process validation studies confirmed that the new strengths can be manufactured consistently within specifications. A comparability study of finished product batches with the proposed new versus the approved old strengths revealed comparability with respect to biological activity, physico-chemical characteristics and impurities.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

Sufficiently detailed data and documents have been provided indicating that the product can be reproducibly manufactured and is adequately controlled.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the quality data provided, the CHMP considers that this extension application to the marketing authorisation for Vihuma is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

Based on the result of a new local tolerance study performed as bridging study to assess the local tolerance of the new vial strengths of Vihuma, e.g. 2500 IU, 3000 IU, 4000 IU, in addition to the already approved strength 2000 IU, it could be concluded that perivenous injections of 0.2 mL/ear of all four Vihuma product strengths tested were well tolerated and did not reveal any test item-related changes at the injection site.

The non-clinical data do not give rise for concern, and are considered to be adequate to support the comparability of the different strengths of Vihuma.

2.4. Clinical aspects

2.4.1. Introduction

No new clinical data have been submitted with this Extension.

Data from Previously Untreated Patients (PUP) from GENA-05 (interim study report) are presented. Additionally, the MAH proposes to collect clinical safety and efficacy data on the new Vihuma product strengths within the frame of the non-interventional GENA-99 post-authorisation study.

2.5. Clinical efficacy

2.5.1. Main study

GENA-05

Study design:

Dosages for on-demand treatment has been chosen to target 40-60% FVIII (dose of 20-30 IU/kg) for minor haemorrhages, 60-80% FVIII (dosage 30-40 IU/kg) for moderate to major haemorrhages, and 100-120% FVIII (40-60 IU/kg) for major to life-threatening haemorrhages. These target FVIII levels are much higher than proposed in the Core SmPC (20-40% for minor, 30-50% for more extensive, and 60-100 for life-threatening haemorrhages). Such “high-dose-regimen” needs to be taken into account when evaluating the positive treatment results.

Recovery investigation: Patients received 40 IU FVIII/kg BW for *in vivo* recovery evaluation. Blood samples were taken at baseline, 15 minutes and 1 hour after the IMP administration. Results are awaited in the Final Study Report and are considered to add significant information for this low age-group with regard to dosage recommendation.

Demographics: About 60 study centres are involved in study GENA-05.

Immunogenicity:

Relevant patient numbers with respect to immunogenicity: According to the interim report, the overall number of subjects with at least one plasma-sample after the first ED was 85. The MAH provided an Interim Report on their PUP-study. Information to be included in section 5.1 of SmPC and into the EPAR as soon as the final study report is available in 2019

Efficacy:

Monthly rate of spontaneous bleeds – as evaluated according to the study protocol is a non-standardised parameter not in accordance with the Clinical Guideline. Bleeding rates, mainly reported as annual bleeding rates (ABR) are not based upon similar definitions (spontaneous bleeds, joint-bleeds, all bleeds?), are not based upon similar conditions (e.g. with or without the opportunity of “preventive” treatment), and are therefore not comparable with study-data of other replacement products. Description in the SmPC or EPAR is therefore not supported, currently.

Assessment of efficacy for a bleeding episode was described to be excellent in 62.2%, good in 29.6%, moderate in 7.6% and none on 0.7% of BEs. Most bleeds (93.2%) resolved with 1-2 days treatment. Mean dose per episode per ED was 48.3 IU/kg. According to the Clinical guideline, efficacy should be reflected as consumption (FVIII/kg) per complete bleeding episode in on-demand patients and prophylaxis patients. If meaningful, stratification of different bleeding types (e.g. joint-bleeds or

gastrointestinal bleeds) might be added. Furthermore, consumption per interval (FVIII/kg per month and per year) should be provided for subjects on prophylaxis and – if meaningful – for on-demand patients in comparison. Consumption in surgeries (Factor VIII/kg per surgical procedure) should be presented, in addition. As proposed for consumption in bleeding episodes, consumption in surgeries might be stratified (e.g. minor and major surgeries), if meaningful. The results should derive from the targeted 100 patients with a target of 100 EDs as awaited within the Final CSR for reflection in the EPAR.

Safety:

Safety-profile – as far as available at the current timepoint – does not deviate from the established profile known from similar FVIII concentrates. However, besides FVIII-inhibition, AEs from the "allergic" complex have been reported in about 20 patients. Symptoms cover rashes, skin rashes urticarial rashes, allergic dermatitis, wheezing, hypersensitivities, acute obstructive bronchitis etc. For further evaluation the MAH is asked to use an adequate search-category (e.g. Standardized MedDRA Queries "anaphylactic reaction" and "hypersensitivity") and analyse reported AEs with interval from last FVIII-infusion to onset of respective AE.

2.5.2. Conclusions on the clinical efficacy and safety

No new clinical data have been submitted with this extension application which is justified by the MAH based on comparability data investigating the old and the new strengths and supported by the results of the local tolerance study. This is considered acceptable.

The submitted documents are essentially in line with the submitted and agreed documents of the extension application X/20, the variation II/17/G and the Article 31 Referral for the reference product Nuwiq. Additionally, the MAH stated that all changes as made to Vihuma are identical to those made for Nuwiq.

Therefore, the assessment of the Extension application X/20 and the variation II/17G as made for Nuwiq is also acceptable for Vihuma.

The submitted product information is in line with the recommendations done by PRAC in the EMA Article 31 Referral and with the agreed product information of Nuwiq (approved with X/20).

Overall, all changes as made for Vihuma with this grouped extension application are identical to those made for Nuwiq with referenced procedures and are considered acceptable.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Inhibitor development (antibodies against rhFVIII) Hypersensitivity reactions, including anaphylactic reactions Cardiovascular events
Important potential risks	Thromboembolic events Medication error including safety in home therapy setting
Missing information	Safety in previously untreated patients Children < 2 years Safety in pregnant or breastfeeding women Immune tolerance induction (ITI)

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
GENA-05 Interventional clinical study (category 3)	Investigate immunogenicity, efficacy and safety of Human cl rhFVIII in PUPs	- Inhibitor development - Safety in PUPs, including children < 2 years - Immune tolerance induction (ITI)	Started in Q1 2013	**Milestone:** Post-approval commitment to follow up at least 100 PUPs (50 from efficacy/safety trial and 50 new) for a minimum of 100 EDs. Final report planned for 2019. One interim analysis - After 50 patients achieved at least 50 EDs
GENA-15	Investigate immunogenicity,	- Inhibitor	Started in	Final report planned for

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
Interventional clinical study (category 3)	efficacy and safety of Human-cl rhFVIII in patients who completed study GENA-05 in accordance with the study protocol	development	Q1 2014	Q4 2019.
GENA-99 Post-marketing study (category 3)	Product safety and clinical efficacy	- Inhibitor development - Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events - Medication error including safety in home therapy setting - Safety in children < 2 years	Started in January 2016	Final report planned for 2020. One study progress report planned two years after marketing authorisation approval. Afterwards yearly status reports will be prepared.
European Haemophilia Safety Surveillance (EUHASS) (category 3)	Product safety	- Inhibitor development - Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events - Medication error including safety in home therapy setting	Ongoing	Octapharma will receive regular product-specific reports. Relevant information included in these reports will be provided in PSURs/PBRERs.

Risk minimisation measures

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Conclusion

It was concluded by the CHMP Rapporteur that this RMP version has already been considered acceptable for Nuwiq by the CHMP and PRAC. The objective of the current submission for Vihuma is to align the content in a single harmonised worldwide version for simocotocg alfa.

The CHMP and PRAC considered that the risk management plan version 10 is acceptable.

2.7. Pharmacovigilance

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.

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.

2.8. Product information

2.8.1. 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 as the proposed text changes are only minor and do not affect the readability.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vihuma (simoctocog alfa) is included in the additional monitoring list as it contains a new active substance which, on 22 May 2014, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Benefit-risk assessment and discussion

The MAH applied for an extension application to add new strengths of 2500 IU, 3000 IU and 4000 IU, powder and solvent for solution for injection grouped with variations to update sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from Previously Untreated Patients (PUP) from GENA-05 (interim report) study, to update the Product Information with the wording agreed in the Art. 31 referral and finally to update the Risk Management Plan (version 10) to align the content in a single harmonised worldwide version for simocotocg alfa (rFVIII).

The submitted documents are essentially in line with the submitted and agreed documents of the extension application X/20, the variation II/17/G and the Article 31 Referral for the reference product Nuwiq. Additionally, the MAH stated that all changes as made to Vihuma are identical to those made for Nuwiq. Therefore, the assessment of the Extension application X/20 and the variation II/17G as made for Nuwiq is also valid for Vihuma.

The MAH provided an Interim Report on their PUP-study. Information to be included in section 5.1 of SmPC and into the EPAR as soon as the final study report is available in 2019

For adequate assessment especially of borderline or transient inhibitor cases, clinical signs of increased factor-consumption (dosage, number of injections), increased bleeding episodes or reduced recovery should be provided for the respective subjects within the final study report. Preliminary data regarding efficacy and safety is considered to be in line with previously collected data in children but should be updated, accordingly, as soon as the final study report is available.

In general, it is recommended to await the final study report for producing reliable results regarding recovery, efficacy, surgery and safety. Consequently, section 4.2 has been updated and Section 4.8 of the SmPC has been updated to add “Hypersensitivity”.

3.2. Conclusions

The overall B/R of Vihuma is positive for these new strengths and grouped variations.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Vihuma new strengths, is favourable in the following indication:

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Vihuma can be used for all age groups.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Vihuma 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 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.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA and IIIB
C.I.1.b	C.I.1.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union referral procedure - The product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	Type IB	I and IIIB

Extension application to add new strengths of 2500 IU, 3000 IU and 4000 IU, powder and solvent for solution for injection.

The above line extension is grouped with the following variations:

- C.I.4 - to update sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from Previously Untreated Patients (PUP) from GENA-05 (interim report) study
- C.I.11.b - to update the Risk Management Plan (version 10) to align the content in a single harmonised worldwide version for simocotcog alfa (rFVIII).
- C.I.1.b - to update the Product Information with the wording agreed in the Art. 31 referral (EMEA/H/A-31/1448).