15 December 2016
EMA/CHMP/814221/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vihuma

International non-proprietary name: simoctocog alfa

Procedure No. EMEA/H/C/004459/0000

Note

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

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Administrative information

Name of the medicinal product:	Vihuma
Applicant:	Octapharma AB Lars Forssells gata 23 112 75 Stockholm SWEDEN
Active substance:	SIMOCTOCOG ALFA
International Non-proprietary Name/Common Name:	simoctocog alfa
Pharmaco-therapeutic group (ATC Code):	B02BD02 - Coagulation factor VIII
Therapeutic indication(s):	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Vihuma can be used for all age groups.
Pharmaceutical form(s):	Powder and solvent for solution for injection
Strength(s):	250 IU, 500 IU, 1000 IU and 2000 IU
Route(s) of administration:	Intravenous use
Packaging:	Powder: vial (glass); Solvent : pre-filled syringe (glass)
Package size(s):	1 vial (powder) + 1 pre-filled syringe (solvent) + 1 vial adapter + 1 needle + 2 swabs

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List of abbreviations

BE: Bleeding Episode

CHMP: Committee for Medicinal Products for Human Use

EC: European Commission

EMA: European Medicines Agency

EPAR: European Public Assessment Report

EU: European Union

ITI: Immune tolerance induction

PDCO: Paediatric Committee

PIP: Paediatric Investigation Plan

PTPs: Previously Treated Patients

PUPs: Previously Untreated Patients

pD: Plasma-derived

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Octapharma AB submitted on 28 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Vihuma, through the centralised procedure. As this application concerns active substance(s) already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 26 May 2016.

The applicant applied for 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 legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Octapharma AB allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Nuwiq authorised on 24 July 2014 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0214/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001024-PIP01-10-M01 was not yet completed as some measures were deferred. The PDCO discussed the completed studies on EMEA-C1-001024-PIP01-10-M01 and considered that these are compliant with the latest Agency's Decision (P/0214/2012) of 28 September 2013.

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 applicant 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 applicant received Scientific Advice from the CHMP on 19 November 2015. The Scientific Advice pertained to quality development of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 28 September 2016.
- The procedure started on 17 October 2016.
- The CHMP and PRAC Rapporteurs' joint Assessment Report was circulated to all CHMP members on 21st November 2016.
- During the PRAC meeting on 1st December, endorsed the relevant sections of the joint CHMP/PRAC Assessment Report.
- During the meeting on 15 December 2016, 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 Vihuma.

2. Scientific discussion

2.1. Introduction

Haemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation factor VIII (FVIII) in sufficient quantities to achieve satisfactory haemostasis. The incidence of congenital haemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%). This deficiency in FVIII predisposes patients with haemophilia A to recurrent bleeding episodes (BEs) in joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Without adequate treatment, these repeated haemarthroses and haematomas lead to long-term sequelae with severe disability. Other less frequent, but more severe bleeding sites, are the central nervous system, the urinary or gastrointestinal tract, eyes and the retro-peritoneum. Patients with haemophilia A are at high risk of developing major and life-threatening BEs after surgical procedures, even after minor procedures such as tooth extraction.

The development of cryoprecipitate and subsequently FVIII concentrates, obtained by fractionation of human plasma, provided replacement FVIII and greatly improved clinical management and life expectancy of patients with haemophilia A. Replacement therapy with exogenous FVIII successfully adjusts haemostasis in these patients, temporarily. Prophylaxis with FVIII concentrates is currently the preferred treatment regimen for patients with severe haemophilia A, especially in very young patients. The majority of patients receiving prophylaxis are treated 3-times weekly or every other day at a dose of 25–40 international units (IU)/kg (or

15–25 IU/kg in an intermediate dose regimen), although an escalating dose regimen is also used. However, on-demand treatment is still the predominant replacement approach in many countries.

The most serious complication in the treatment of haemophilia A is the development of neutralising antibodies (inhibitors) against FVIII, rendering the patient resistant to replacement therapy and thereby increasing the risk of unmanageable bleeding events, particularly arthropathy and disability.

Vihuma is a recombinant B-domain-deleted (BDD) rFVIII human FVIII concentrate that is produced in genetically modified human embryonic kidney (HEK) 293F cells. The rationale for using a human cell line for rFVIII expression was in order to more closely mimic the pattern of post-translational modifications (PTMs) of endogenous FVIII, resulting in elimination of potentially antigenic epitopes created during production in non-human cells. *N*-glycosylation of Vihuma shows the same distribution of *N*-glycosylation types outside the FVIII B-domain as human plasma-derived FVIII (pdFVIII). The only type of sialic acid present is *N*-acetylneuraminic acid (Neu5Ac). The sialic acid *N*-glycolylneuraminic acid (Neu5Gc), reported to be antigenic in man, was not detected.

Vihuma is presented as lyophilised powder and is reconstituted with 2.5 mL of sterilised water for injections in a syringe in single-dose vials containing 250 IU, 500 IU, 1000 IU, and 2000 IU of recombinant factor VIII per vial.

2.2. Quality aspects

2.2.1. Introduction

Reference has been made to data provided in Module 3 for Nuwiq and no additional data have been provided. Since this application is an informed consent of the Nuwiq application, the quality data in support of the Vihuma application are identical to the up-to-date quality data of the Nuwiq dossier, which have been assessed and approved, including all post-marketing procedures.

2.2.2. Conclusions on the chemical, pharmaceutical and biological aspects

In this informed consent application, there are no new issues related to the quality data. All the quality data have been assessed for Nuwiq application and adequately reflected in the Product Information. The ongoing recommendations for future quality development for Nuwiq are applicable to Vihuma.

2.3. Non-clinical aspects

2.3.1. Introduction

Reference has been made to data provided in Module 4 for Nuwiq and no additional studies have been provided. Since this application is an informed consent of the Nuwiq application, the non-clinical data in support of the Vihuma application are identical to the up-to-date non-clinical data of the Nuwiq dossier, which have been assessed and approved, including all post-marketing procedures.

2.3.2. Ecotoxicity / environmental risk assessment

The applicant has referred to the Environmental Risk Assessment for Nuwiq. According to the "Guideline on the environmental risk assessment of medical products for human use" substances like amino acids, peptides, proteins, carbohydrates and lipids are exempted from the guideline since they are unlikely to result in significant risk to the environment. *Human-cl rhFVIII* is a polypeptide and thereby exempted, consequently, an environmental risk assessment is not required. Marketing of Vihuma in the European Union is not expected to increase the environmental risk.

2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no new issues related to the non-clinical data. All the non-clinical data have been assessed in the application for reference medicinal product, Nuwiq and adequately reflected in the Product Information.

2.4. Clinical aspects

2.4.1. Introduction

Reference has been made to data provided in Module 5 for Nuwiq and no additional studies have been provided. Since this application is an informed consent of the Nuwiq application, the clinical data in support of the Vihuma application are identical to the up-to-date clinical data of the Nuwiq dossier, which have been assessed and approved, including all post-marketing procedures.

2.4.2. Conclusions on the clinical efficacy

In this informed consent application, there are no new issues related to the clinical data. All the clinical data have been assessed for Nuwiq application and adequately reflected in the Product Information.

2.5. Risk Management Plan

Safety concerns

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

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] 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 Nuwiq/Vihuma in PUPs	- Inhibitor development - Safety in PUPs, including children < 2 years - Immune tolerance induction (ITI)	Started in Q1 2013	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. Two interim analyses planned: - After 30 patients started treatment - After 50 patients achieved at least 50 EDs
GENA-13 Interventional clinical study (category 3)	Determine the long-term immunogenicity and tolerability of Nuwiq/Vihuma	- Inhibitor development - Hypersensitivity reactions, including anaphylactic reactions	Started in Q4 2011	Final report planned for Q4 2016.
GENA-15 Interventional clinical study (category 3)	Investigate immunogenicity, efficacy and safety of Nuwiq/Vihuma in patients who completed study GENA-05 in accordance with the study protocol	- Inhibitor development	Started in Q1 2014	Final report planned for Q4 2019.
GENA-99 Post-marketing study (category 3)	Product safety and clinical efficacy	Inhibitor development - Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events	Ongoing	Final report planned for 2020. One study progress report planned two years after marketing authorisation

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of interim or final reports (planned or actual)
		- Medication error including safety in home therapy setting - Safety in children < 2 years		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.

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Inhibitor development (antibodies against rhFVIII)	Mentioned in the SmPC (Sections 4.2, 4.4 and 4.8)	*None*
Hypersensitivity reactions, including anaphylactic reactions	Mentioned in the SmPC (Sections 4.3, 4.4 and 4.8)	None
Thromboembolic events	Mentioned in the SmPC (Section 4.4)	None
Medication error including safety in home therapy setting	Mentioned in the SmPC (Sections 4.2 and 4.9)	None

	Mentioned in the PIL (Section 3)	
Previously untreated patients	Mentioned in the SmPC (Section 4.2)	None
Children < 2 years	Mentioned in the SmPC (Sections 4.2, 4.4 and 4.8)	None
Immune tolerance induction (ITI)	Mentioned in the SmPC (Section 4.4)	None
Pregnant or breast feeding Women	Mentioned in the SmPC (Section 4.6)	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The applicant has submitted a Risk Management Plan RMP and states that it is the same RMP as the currently approved RMP for Nuwiq.

The CHMP and PRAC considered that the risk management plan version 5.3 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

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

2.7. Product information

The Product information of Vihuma is identical to the Nuwiq product information. Only the name of the medicinal product is different and addresses of Biotest AG are listed as local representatives in the Package Leaflet instead of Octapharma AB.

Consultation with target patient groups

The applicant states in Module 1.13, that the package leaflet intended to be used for Vihuma includes the same text as the package leaflet approved for Nuwiq. Therefore, a consultation with target patient groups has not been performed for the package leaflet of Vihuma by the applicant.

Braille

The applicant states in Module 1.13, that the invented name of the medicinal product, followed by its strength is printed on the outer carton in Braille.

2.7.1. 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

This Marketing Authorisation application for Vihuma has been submitted by Octapharma AB. as an informed consent application in accordance with Article 10c of Directive 2011/83/EC, as amended.

As a consequence, quality, safety and efficacy of the Nuwiq medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Vihuma. The application for Vihuma concerns the identical strengths to those approved for Nuwiq and consists of only Module 1. Information on the scientific discussion can be found in the Nuwiq CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

Consequentially, and in line with the assessment of data undertaken in the framework of the Nuwiq initial marketing authorisation application as well as within all post-authorisation procedures, the CHMP considers that the benefit/risk balance for Vihuma is positive.

3.1. Conclusions

The overall B/R of Vihuma is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vihuma 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 granting of the marketing authorisation 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).

Other 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.