CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml, powder and solvent for solution for injection Baxter B.V., the Netherlands

octocog alfa, recombinant coagulation factor VIII

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0043/004-006/MR
Registration number in the Netherlands: RVG 108041, 108043, 108044

21 May 2013

Pharmacotherapeutic group:	octacog alfa, recombinant coagulation factor VIII
ATC code:	B02BD02
Route of administration:	intravenous
Therapeutic indication:	prophylaxis of bleeding in patients with Haemophilia A (congenital Factor VIII deficiency) in all age groups. This product is not indicated in von Willebrand's disease.
Prescription status:	prescription only
Date of first authorisation in NL:	10 July 2012
Concerned Member States:	Mutual recognition procedure with BE, BG, CZ, EE, HU, IT, LT, LV, PL, RO, SK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml, powder and solvent for solution for injection from Baxter B.V. The date of authorisation was on 10 July 2012 in the Netherlands.

The product is indicated for treatment and prophylaxis of bleeding in patients with Haemophilia A (congenital Factor VIII deficiency).
This product does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease. Recombinate is indicated for all age groups from neonates to adults.

A comprehensive description of the indications and posology is given in the SPC.

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. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Recombinate 250 IE, 500 IE and 1000 IE, powder and solvent for solution for injection with 10 ml water for injections (NL License RVG 16030-16032) was first approved in the Netherlands on 13 May 1993 for the treatment and prophylaxis of bleeding in patients with Haemophilia A (congenital Factor VIII deficiency). Subsequently these products were part of MRP NL/H/0043/001-003.
This mutual recognition procedure concerns a line extension to these products for the introduction of 5 ml water for injection (WFI) as diluent for the reconstitution of Recombinate. Per request of patients and health care professionals the option is offered for the reconstitution of the product with 5 ml for all three strengths (250, 500 and 1000 IU) in addition to the currently licensed 10 ml reconstitution volume.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This mutual recognition procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data. The active component of Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml is considered to be well-known and its clinical pharmacology has been extensively studied. Parts of the data in the dossier of Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml were already submitted in the dossier of Recombinate 250 IE, 500 IE and 1000 IE, which is supplied with 10 ml water for injections. The MAH performed three non-clinical studies which investigated the difference between reconstitution of Recombinate in 5 ml or 10 ml concerning pharmacodynamics, pharmacokinetics and toxicology. The MAH has not conducted any new pharmacokinetic studies with the different reconstitution volume. No clinical data are included in support of this line extension. An addendum to the clinical overview was submitted.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
There are no changes to the drug substance, Recombinant Antihemophilic Factor VIII (= rAHF).

Medicinal Product

Composition
Recombinate 250 IU/5 ml contains nominally 250 IU octocog alfa, recombinant coagulation factor VIII per vial. The product contains approximately 50 IU/ml octocog alfa, recombinant coagulation factor VIII, when reconstituted with 5 ml of sterile water for injections.
Recombinate 500 IU/5 ml contains nominally 500 IU octocog alfa, recombinant coagulation factor VIII per vial. The product contains approximately 100 IU/ml octocog alfa, recombinant coagulation factor VIII, when reconstituted with 5 ml of sterile water for injections.
Recombinate 1000 IU/5 ml contains nominally 1000 IU octocog alfa, recombinant coagulation factor VIII per vial. The product contains approximately 200 IU/ml octocog alfa, recombinant coagulation factor VIII, when reconstituted with 5 ml of sterile water for injections.

The product is a white to off-white friable powder. The solvent (sterilised water for injections) is a clear and colourless liquid. The excipients are human albumin, sodium chloride, histidine, macrogol 3350, calcium chloride dehydrate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

A single pack contains a powder vial, a 5 ml solvent vial (both type I glass with rubber stoppers) and a device for reconstitution (BAXJECT II) + one sterile single-use plastic syringe + one sterile mini-infusion set + 2 alcohol swabs + 2 plasters.

Manufacturing process
There are no changes to the Recombinate final drug product or its manufacture compared to the existing Recombinate authorisations.

Control of excipients
The sterilised water for injections (WFI) complies with the requirements of the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The drug product release specifications of drug product reconstituted with 5 ml WFI were amended in accordance with the twofold increase of the concentrations of the excipients, compared to the drug product reconstituted with 10 ml WFI.

Container closure system
The powder vial is the same as the one for the approved Recombinate products. The 5 ml package size for the solvent is filled in quantities of 5.4 ml into glass vials (hydrolytic type I, complying with Ph. Eur.) of 6 ml filling capacity, internally treated with ammonium sulfate. The vials are closed with chlorobutyl rubber stoppers with FluoroTech coating, which comply with Ph.Eur. requirements.

Stability of drug product

Based on the provided stability data of the 5 ml package size of WFI, a shelf life of 2 years when stored at +2 to +8°C. Within its shelf-life, the product may be stored at 15°C - 25°C prior to use for up to six months, but should not be returned to refrigeration following storage at 15°C - 25°.
For the needleless reconstitution BAXJECT II NTD can be used as an alternative to the needle device (filter needle, double ended needle). Sufficient qualification data were provided for the use of both the BAXJECT II NTD and the needle device in reconstitution of the drug product. The final report of a 24 hour reconstitution stability study was provided of two lots of Recombinate, reconstituted with 5 and 10 mL of WFI. The data show no significant differences in stability after reconstitution with WFI 5 ml compared to WFI 10 ml.

Specific measures concerning transmissible agents
The Guideline on the warning on transmissible agents in summary of product characteristics (SPCs) and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1, 15 December 2011) states:
"There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes. When albumin is used as excipient in medicinal products, there is no need to include any specific warning statement related to albumin. This is based on the good safety record of human albumin. In these products, human albumin should be declared in the list of excipients."
In accordance with this guideline, human albumin is included in the list of excipients in the SPC. No safety warning is required.
In the production of Recombinate several substances of animal origin are used. TSE certificates for all these materials have been provided.

II.2 Non-clinical aspects

Pharmacology
The Factor IXa-cofactor activity, thrombin sensitivity and thrombin generating-capacity of a low and a high potency Recombinate lot after reconstituted were compared between 10-ml and 5-ml solvents. The results demonstrated that no differences appear in either measured activity or stability by reducing the solvent amount to 50% of the currently used volume of 10 ml. No effect on the biological function was observed when FVIII activity was measured after incubation and subsequent dilution in physiological buffers or plasma even though both albumin and the excipient concentrations were increased by a factor of 2.

Pharmacokinetics
Effect of Reconstitution Volume on Pharmacokinetics (study PV2160705, GLP)
This study compared the PK profiles of Recombinate reconstituted with 5 ml WFI and 10 ml WFI after a single intravenous dose in rats. Groups of ten male rats were treated with 1000 IU/vial and 250 IU/vial Recombinate reconstituted with 5 ml WFI. The reference groups were treated with the same lots reconstituted with 10 ml WFI. Samples taken prior to infusion and at 5 minutes, 1 hour, 4 hours, 8 hours, 12 hours and 24 hours after intravenous administration at a target dose of 200 IU/kg were analyzed for human Factor VIII antigen using ELISA.

There were no statistical differences in the $AUC_{0\text{-tlast}}$ (24), mean residence time, volume of distribution, initial half-life and terminal half-life between the dosage strengths. Statistically significant differences occurred in both dosage strengths in C_{max} and *in-vivo* recovery, and in the 1000 IU/vial dosage strength in clearance and AUC0-∞ (table 1).

Table 1. Pharmacokinetic parameters in rats

Item	Recon. vol (mL)	Actual dose FVIII Ag U/kg	AUC $_{0\text{-t last}}$ [FVIII AgU* min*kg/mL* FVIII AgU	AUC $_{0\text{-}\infty}$ [FVIII AgU* min*kg/mL* FVIII AgU	C_{max} [FVIII AgU/mL	MRT [min]	Cl [mL* h^{-1}*kg^{-1}	V_{ss} [mL/kg]	IVR [%]	T½ initial [min]
RECOMBINATE #TRH07849AA 1000 IU/vial	10	210.1	3.44	3.69*	0.018*	393.1	0.27	106.58	56.8*	57.0
	5	227.0	2.84	3.06*	0.014*	356.0	0.33	116.21	44.9*	65.8
RECOMBINATE #TRL07821AA 250 IU/vial	10	223.5	3.23	3.37	0.015*	355.4	0.30	105.58	47.4*	88.6
	5	214.6	3.46	3.72	0.018*	370.4	0.27	99.43	56.0*	59.1

* = statistically significant differences

These relatively small differences are likely the result of both the variability of the animal model and the very small injection volumes for rats due to the high concentration of FVIII. Small injection volumes may result in a loss of FVIII activity caused by volume loss associated with injecting small volumes into small animals (e.g. 350 µl for a 350 g rat).

The $AUC_{0\text{-tlast}}$ and the concentration time curves are almost super imposable for both dosage strengths tested, indicating that there is little difference in the PK profiles of Recombinate reconstituted with either 5 ml or 10 ml WFI.

The MEB observed that the PK profiles of Recombinate reconstituted with either 5 ml or 10 ml WFI are almost identical. Some minor but statistically significant differences are probably caused by the variability of the used animal model, are not consistent and are not expected to lead to differences in pharmacology and toxicity of the 5 ml reconstitution compared to the 10 ml reconstitution.

Impact of Volume Loss During Infusion (study 98002-CMC-295R, non-GLP)

Volume losses in infusion sets are normally observed during administration of intravenous products such as Recombinate. The patient dose, as defined by the clinical studies, accommodates these volume losses. The impact of the volume loss on the infusion of a more concentrated Recombinate product (*i.e.* reconstituted with 5 ml WFI as opposed to 10 ml WFI) was evaluated in this study. No significant difference in volume losses associated with the reconstitution volumes (5 ml or 10 ml) was observed in the study.

The MEB noted that no significant difference in volume losses associated with the reconstitution volumes (5 ml or 10 ml) was observed in a study for comparison of two different infusion devices..

Conclusion on pharmacokinetics

In conclusion, no statistical differences were observed in the area-under-the-curve [$AUC_{0\text{-t(last)}}$], mean residence time (MRT), Volume of distribution at steady state (V_{ss}), and initial/terminal half-life. Small, however statistically significant differences were observed in the maximal concentration (C_{max}), *in-vivo* recovery, clearance (CL) and $AUC_{0\text{-}\infty}$ between Recombinate reconstituted in 10 ml and 5 ml water for injections (WFI).

Toxicology

Effect of Reconstitution Volume on Local Tolerance in Rabbits (study PV2180701, GLP)

The impact of the increase in excipient concentration was evaluated in a well-established rabbit model used to evaluate tissue irritation. Local irritation resulting from intravenous (clinical application route), intra-arterial and paravenous (possible misapplication routes) infusion in rabbits of 250 and 1000 IU/vial Recombinate reconstituted with either 5 ml or 10 ml WFI was compared to a vehicle control (i.e. the respective buffer solutions without Factor VIII). Each item was either injected intravenously or intra-arterially at a volume of 5 ml per animal (within 2 minutes), or injected paravenously at a volume of 0.5 ml per animal (bolus injection) into the right ear of each of four rabbits (2 male, 2 female) resulting in a total of 72 tested animals. An equivalent volume of isotonic saline was given as a negative control to the left ear of every rabbit.

No changes could be seen macroscopically after intravenous administration regardless of the reconstitution volume or the dosage strength tested. After intra-arterial administration and after paravenous injection (possible misapplication routes) short term, slight tissue irritation was observed macroscopically in some tested animals, probably caused by the injection procedure itself (intra-arterial administration) and increased excipient (paravenous route).

The MEB noted that all dosage strengths of Recombinate reconstituted with 5 ml WFI were well tolerated after intravenous administration. Misapplication (intra-arterially or paravenously) may cause a very mild, short-term tissue reaction, however not leading to any adverse histopathological consequences.

Conclusion on toxicology
Recombinate reconstituted in 10 ml or 5 ml WFI was generally well tolerated when injected intravenously. Mild, short-term local tissue irritation was observed, however, with the 5 ml product and buffer when injected intra-arterially or paravenously, indicating that there is a potential for the occurrence of mild local injection site reactions, such as erythema, stinging due to extravasation. No macroscopic or histopathological changes were observed with any test article or infusion route.

Conclusions
The MAH performed three non-clinical studies which sufficiently demonstrated that there is no relevant difference between reconstitution of Recombinate in 5 ml or 10 ml concerning pharmacodynamics, pharmacokinetics and toxicology.

Environmental risk assessment
A declaration has been submitted that no special environmental risk assessment is required because the use, storage and disposal of the medicinal product do not include any potential risk for the environment. The medicinal product contains electrolytes and proteins which are exempted according to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) because they are unlikely to result in significant risk to the environment. Furthermore, no genetically modified organisms (GMOs) are contained in Recombinate. This rationale is agreed.

II.3 Clinical aspects

No clinical data are included in support of this line extension. An addendum to the clinical overview was submitted, which includes no new clinical data and no new references.

The introduction describes the purpose of this line extension application which is to propose an alternate reconstitution volume, allowing patients to reconstitute the Recombinate with 5 m of WFI prior to infusion. There are no changes to the Recombinate final drug product as a result of this change. The purpose and rationale for the 5 ml reconstitution volume is well described. Dilution with 5 ml of WFI in stead of 10 ml will result smaller infusion volume and faster infusion times. This is more convenient for patients and may lead to a lower risk of extravasation problems . There are no major safety concerns to be expected except for mild infusion site reactions.

The Factor VIII concentration for the highest dosage strength (1000 IU) of Recombinate reconstituted with 5 ml (200 IU/ml) is lower than the Factor VIII concentration in 3000 IU/vial (600 IU/ml) of another Factor VIII containing product, Advate. Advate 250 IU, 500 IU, 1000 IU and 1500 IU, 2000 IU and 3000 IU has been registered through a centralized procedure by Baxter AG since 2 March 2004 (EU license number EU/1/03/271/001-006). No changes are proposed in the infusion rate described in the labeling. While the rate of Factor VIII infusion increases in Recombinate reconstituted using 5 ml WFI compared to the 10 ml WFI, this is again less than the rate of Factor VIII infusion utilized in currently available Advate. Advate shows no important adverse events except for mild infusion site reactions.

A comparative clinical study with Recombinate diluted with 5 ml of 10 ml WFI is not required in view of:
- the lower concentration compared to Advate, which is a frequently used product that has limited side effects besides mild local injection site reactions.

- the comparative study with Recombinate reconstituted in 10 ml or 5 ml WFI in rabbits, which was generally well tolerated, indicated no relevant differences in pharmacokinetics between the two dilutions, showed only mild local injection site reactions, such as erythema, stinging due to extravasation and no permanent macroscopic or histopathological changes with any test article or infusion route.

In conclusion, the clinical overview including an addendum is considered acceptable. The option for reconstitution of the product with 5 ml for all three strengths (250, 500 and 1000 IU) in addition to the currently licensed 10 ml reconstitution volume is considered legitimate.

Risk management plan
The MAH has a pharmacovigilance system at their disposal. A commitment was made to submit a variation concerning the change from the Detailed Description of the Pharmacovigilance System (DDPS) to the Summary of Pharmacovigilance System Master File (PSMF) in accordance with the requirements of Directive 2001/83/EC as amended.
With the exception of the information regarding non-clinical Study PV2180701 (evaluating tissue irritation in rabbits from infusion of Recombinate reconstituted with either 5 ml WFI or 10 ml WFI), there were no significant additions to the RMP with regard to the introduction of 5 ml water for injection (WFI) as diluent for the reconstitution of Recombinate.

Product information

SPC
The product information has been based on the already authorized Recombinate products (NL/H/0043/001-003/MR) with 10 ml WFI, with changes only relevant to the 5 ml WFI.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. These results show that the percentage of participants successfully finding the section and answering the questions correctly was within the acceptable percentage outlined in the protocol and was 90% or more.
General comments on the format and layout of the leaflet were positive indicating that participants were able to find the required information and understand it. The overall observational conclusion was that the results of the interviews showed that the PIL for Recombinate could be rated as readable and comprehensible. No changes were made to the PIL during the user testing process therefore no further testing is required. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml, powder and solvent for solution for injection have a proven chemical-pharmaceutical quality and are legitimate line extensions to Recombinate 250 IE, 500 IE and 1000 IE, powder and solvent for solution for injection with 10 ml water for injections (NL License RVG 16030-16032).

Per request of patients and health care professionals the option is offered for the reconstitution of the product with 5 ml for all three strengths in addition to the currently licensed 10 ml reconstitution volume.

Three non-clinical studies sufficiently demonstrated that there is no relevant difference between reconstitution of Recombinate in 5 ml or 10 ml concerning pharmacodynamics, pharmacokinetics and toxicology.

The clinical overview including an addendum is considered acceptable. The option for reconstitution of the product with 5 ml for all three strengths (250, 500 and 1000 IU) in addition to the currently licensed 10 ml reconstitution volume is considered justified, as the concentration is lower compared to Advate, which is a frequently used product that has limited side effects. Furthermore, comparative studies were conducted with Recombinate reconstituted in 10 ml or 5 ml WFI in rats and rabbits indicating no relevant differences in pharmacokinetics between the two dilutions and showing only mild local injection site reactions and no permanent macroscopic or histopathological changes, respectively.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with the SPC for already authorized Recombinate products.

The Board followed the advice of the assessors. Recombinate 250 IE/5 ml, 500 IE/5 ml and 1000 IE/5 ml, powder and solvent for solution for injection were authorised in the Netherlands on 10 July 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 12 February 2013.

The PSUR submission cycle is three-yearly. The next data lock point is 28 February 2014.

The date for the first renewal will be: 10 July 2017.

The following post-approval commitments have been made during the procedure:

Pharmacovigilance system

- The MAH committed to change the name of Recombinate which is reconstituted with 10 ml WFI to Recombinate 250 IU/10 ml, Recombinate 500 IU/10 ml and Recombinate 1000 IU/10 ml after the Recombinate 5 ml line extension in order to distinguish it from Recombinate 250 IU/5 ml, Recombinate 500 IU/5 ml and Reeombinate 1000IU/5 ml.
- The MAH committed to submit a variation concerning the change from the Detailed Description of the Pharmacovigilance System (DDPS) to the Summary of Pharmacovigilance System Master File (PSMF) in accordance with the requirements of Directive 2001/83/EC as amended.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
WFI	Water for Injections

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached