20 July 2023
EMA/358639/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esperoct

International non-proprietary name: Turoctocog alfa pegol

Procedure No. EMEA/H/C/004883/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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List of abbreviations

All abbreviations used are explained in the text.

1. Background information on the procedure

1.1. Submission of the dossier

Novo Nordisk A/S submitted on 12 September 2022 an extension of the marketing authorisation.

The MAH applied for an addition of two new strengths, 4000 IU and 5000 IU.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(c) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable.

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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because no other authorised orphan medicinal product was approved for a condition related to the proposed indication.

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: Daniela Philadelphy Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: N/A

The application was received by the EMA on	12 September 2022
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 December 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 January 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 March 2023
The CHMP Rapporteurs circulated the CHMP Assessment Report on the responses to the List of Questions to all CHMP members on	3 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	25 May 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	20 June 2023
The CHMP Rapporteurs circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	03 July 2023
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 Esperoct on	20 July 2023

2. Scientific discussion

2.1. About the product

Turoctocog alfa pegol is a purified recombinant human factor VIII (rFVIII) product with a 40 kDa PEG conjugated to the protein. The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII (turoctocog alfa). The PEGylation increases the half-life of the protein.

The mechanism of action for turoctocog alfa pegol is based on the replacement of the deficient or absent FVIII in patients with haemophilia A. When turoctocog alfa pegol is activated by thrombin at the site of injury, the pegylated truncated B-domain is cleaved off, generating activated FVIII (FVIIIa), which is similar in structure to native FVIIIa. Activated rFVIII acts as a cofactor for activated factor IX (FIX) on the surface of activated platelets and the complex catalyses the activation of factor X. By adding FVIII, the coagulation cascade can run uninterruptedly ensuring that the end product, fibrin, is generated and a haemostatic plug is formed.

Esperoct is currently marketed in five strengths (500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU). The turoctocog alfa pegol finished product is a lyophilised powder for reconstitution into a solution for injection for intravenous use.

The Line Extension concerns the introduction of new strengths (4000 and 5000 IU) and the change is related solely to the finished product as only the amount of active substance is changing, while the excipients amount is the same as for the marketed strengths of Esperoct.

2.2. Type of Application and aspects on development

Esperoct is currently approved in five strengths (500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU). This extension of marketing authorisation concerns the addition of two new strengths (4000 and 5000 IU).

2.3. Quality aspects

2.3.1. Introduction

Esperoct is currently marketed in five strengths (500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU). The turoctocog alfa pegol finished product is a lyophilised powder for reconstitution into a solution for injection for intravenous use. The finished product is for single use administration. The lyophilised turoctocog alfa pegol finished product is reconstituted in 4.3 mL 0.9% sodium chloride solution before use. The withdrawal volume is 4 mL.

This Line Extension (LE) concerns the introduction of two new strengths (4000 IU and 5000 IU) and the change is related solely to the finished product as only the amount of active substance is changing, while the excipients amount is the same as for the marketed strengths of Esperoct.

There is no change affecting the active substance (turoctocog alfa pegol) and it is the same active substance as the already marketed strengths of Esperoct. Moreover, for new strengths (4000 and 5000 IU) the finished product manufacturing process, the analytical procedures (validated), the device component and the container closure system (besides the cap colour) remain the same as approved for the marketed strengths of Esperoct. Based on the above, it has been agreed that a Notified Body opinion is not required for this LE.

2.3.2. Active Substance

2.3.2.1. General information

Turoctocog alfa pegol is a purified recombinant human factor VIII (rFVIII) product with a 40 kDa PEG conjugated to the protein. The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII (turoctocog alfa). The PEGylation increases the half-life of the protein. The rFVIII (turoctocog alfa) active substance intermediate is expressed in Chinese Hamster Ovary host cells. The molecular mass of the turoctocog alfa pegol protein part is 166 kDa. The molecule consists of a heavy chain of 87 kDa and a light chain of 79 kDa held together by non-covalent interactions. The molecular mass of turoctocog alfa pegol is 216 kDa including post-translational modifications and the PEG moiety.

The mechanism of action for turoctocog alfa pegol is based on the replacement of the deficient or absent FVIII in patients with haemophilia A. When turoctocog alfa pegol is activated by thrombin at the site of injury, the pegylated truncated B-domain is cleaved off, generating activated FVIII (FVIIIa), which is similar in structure to native FVIIIa. Activated rFVIII acts as a cofactor for activated factor IX (FIX) on the surface of activated platelets and the complex catalyses the activation of factor X. By adding FVIII, the coagulation cascade can run uninterruptedly ensuring that the end product, fibrin, is generated and a haemostatic plug is formed. PEGylation increases the half-life of the protein.

There is no change affecting the active substance (turoctocog alfa pegol) and it is the same active substance as the already marketed strengths of Esperoct. The active substance is identical to the already approved active substance for Esperoct and the majority of the active substance module 2 and module 3 documents remain unchanged compared to documentation previously submitted and approved. Consequently, only those sections in the active substance part are briefly discussed where changes have been implemented.

2.3.2.2. Manufacture, characterisation and process controls

There are no changes to the section of the module.

2.3.2.3. Specification

The description of the analytical procedure SE-HPLC (size exclusion-high-performance liquid chromatography) has been updated with the new strengths (4000-5000 IU) information. These amendments in the method description are acceptable and no concerns are raised.

2.3.2.4. Stability

There are no changes to the section of the module.

2.3.3. Finished Medicinal Product

For the new strengths (4000 and 5000 IU) the finished product manufacturing process, the analytical procedures (validated), the device component and the container closure system (besides the cap colour) remain the same as approved for the marketed strengths of Esperoct.

2.3.3.1. Description of the product and pharmaceutical development

The turoctocog alfa pegol finished product is a lyophilised powder for reconstitution into a solution for injection for intravenous use. The finished product is for single use administration.

The vial for the five product presentations of turoctocog alfa pegol finished product is a 5 mL vial made of type I glass, high hydrolytic resistance, in compliance with Ph. Eur., USP and JP. The lyophilised turoctocog alfa pegol finished product is reconstituted in 4.3 mL 0.9% sodium chloride solution in a prefilled syringe before use. A vial adapter is provided for turoctocog alfa pegol finished product. It is a fluid transfer device that allows for the easy transfer of fluids. The vial adapter is a sterile, disposable device packed in a blister package.

The turoctocog alfa pegol finished product was developed in five strengths containing 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. The product line is now extended with two additional strengths containing 4000 IU and 5000 IU of turoctocog alfa.

The composition of the turoctocog alfa pegol finished product is the same for the seven presentations (500 IU – 5000 IU) except for the content of the active substance.

Table 1. Finished product composition

Component	Function	Reference to standards
Active ingredient		
Turoctocog alfa pegol drug substance: 500 IU/vial drug product 1000 IU/vial drug product 1500 IU/vial drug product 2000 IU/vial drug product 3000 IU/vial drug product **4000 IU/vial drug product** **5000 IU/vial drug product**	Active ingredient	Novo Nordisk
Excipients		
L-Histidine	Buffer	Ph. Eur., USP, JP
Sucrose	Stabiliser	Ph. Eur., USP, JP
Polysorbate 80	Surfactant	Ph. Eur., USP, JP
Sodium chloride	Stabiliser	Ph. Eur., USP, JP
L-Methionine	Anti−oxidant	Ph. Eur., USP, JP
Calcium chloride dihydrate	Stabiliser	Ph. Eur., USP, JP
Hydrochloric acid	pH adjustment	Ph. Eur., USP, JP
Sodium hydroxide	pH adjustment	Ph. Eur., USP, JP
Water for injections	Solvent	Ph. Eur., USP, JP

The development of the additional 4000 IU and 5000 IU strengths have been appropriately addressed and the relevant sections in P.2 Pharmaceutical Development have been updated. No changes except the addition of the 4000 and 5000 IU/vial strengths have been implemented. Only the amount of active substance is changing, while the excipients amount is the same as for the marketed strengths of Esperoct. Moreover, for new strengths the device component, the container closure system (besides the cap colour) and the reconstitution diluent in a prefilled syringe remain the same as approved for the already marketed strengths of Esperoct.

The finished product manufacturing process for the 4000 and 5000 IU strengths has not changed. To further support the implementation of two new product strengths the stability data for the strengths 500 IU, 1000 IU, 2000 IU and 3000 IU are compared to data for the new strengths 4000 IU and 5000 IU. These data support the MAH's conclusion that the development in degradation products is comparable for all batches. The batch release results for turoctocog alfa pegol new strengths (4000 IU - 5000 IU) finished product is all within the finished product specification. The results are also comparable across the seven strengths of turoctocog alfa pegol finished product, except for some test parameters which are different for each strength depending on the amount of active substance. It can be agreed that comparability of new strengths versus the initially approved strengths has been shown.

With respect to the compatibility studies of reconstituted turoctocog alfa pegol finished product in contact with the vial adapter and in contact with the syringe for administration, the MAH justified, during the assessment, that a different behaviour of the protein solutions at the higher concentration is not expected.

2.3.3.2. Manufacture of the product and process controls

The section 'Manufacture' has been appropriately addressed. The manufacturing facilities for production and quality control of turoctocog alfa pegol finished product formulated as 4000 IU and 5000 IU/vial strengths are the same as for the approved 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU/vial strengths.

The batch formula has been updated to include the 4000 IU and the 5000 IU strength, the composition is identical for all strengths except for the content of the active substance.

The standard procedures for manufacturing of a lyophilised parenteral in the commercial facility comprises the consecutive sequence of processes for: 1) thawing of active substance, 2) compounding of finished product, 3) sterile filtration, 4) filling, 5) lyophilisation, 6) capping and 7) visual inspection. During the manufacturing process a series of process control (controls of process parameters and in-process test) with defined limits are performed to ensure the quality of the finished product. In summary, the finished product manufacturing process and its controls remains essentially unchanged except that the sampling strategy for quality control is changed and that the bioburden limits are changed. This is acceptable. In addition, a few editorial changes were made in this section.

The turoctocog alfa pegol manufacturing process is already validated for the 500 IU - 3000 IU strengths in a batch size range. A full-scale manufacturing validation has been performed for the manufacturing process of turoctocog alfa pegol finished product with the two new strengths of 4000 IU and 5000 IU in the commercial facility licensed for commercial production. The full–scale manufacturing validation of 4000 IU - 5000 IU is supplemental to the existing validation resulting in a validation product range of 500 - 5000 IU in a batch size range based on identical manufacturing process and product sameness. Sameness applies to the manufacturing process and process design for turoctocog alfa pegol as all strengths have the same, excipient composition, manufacturing process and process controls, sterile filters, vial size and filling volume per vial, lyophilisation programme, and primary packaging and container closure system.

Validation of 4000 IU and 5000 IU is performed and provides documented evidence that the process, when operated within the established parameters, can perform effectively and reproducible to produce product that meets the predetermined specifications and quality attributes.

The sampling programme for the validation batches consisted of routine sampling for process control, release specification testing, and supplementary sampling to provide documentation of quality and chemical stability

of finished product during compounding and during filling and to provide documented evidence of the product quality and batch uniformity after lyophilisation.

All acceptance criteria have been fulfilled within the described limits for routine process controls and supplementary sampling.

The results for the strengths 4000 IU and 5000 IU were comparable to the results for the strengths 500 IU - 3000 IU. In summary, the MAH's conclusion that the consecutive validation batches demonstrated a high level of process reproducibility and consistency both in terms of the routine process controls and the analytical results of the supplementary sampling programme can be agreed.

2.3.3.3. Product specification

No changes to the finished product specifications have been implemented except the updates with the new strengths. These updates for the 4000 IU and 5000 IU include strength-specific specification limits. These limits are based on the specification limits for the existing strengths and can be agreed on.

Analytical procedures

The analytical procedures are unchanged as the ones approved for the marketed strengths and have been validated for the new strengths. Supplementary validation was performed. This strategy is acceptable and agreed.

Batch analysis

Batch data obtained for the new strengths of turoctocog alfa pegol finished product batches, 4000 IU and 5000 IU at release have been submitted.

The batch release results for turoctocog alfa pegol new strengths (4000 IU - 5000 IU) finished product are all within the finished product specification and confirm that the finished product manufacturing process can manufacture finished product with the new, higher strengths consistently meeting its predetermined quality standards.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D is included in the dossier.

Appropriate documentation on the conducted nitrosamine risk assessment has been provided. The MAH`s conclusion that no risk of presence of nitrosamines in the active substance and finished product has been identified is supported.

2.3.3.4. Stability of the product

The MAH claims a shelf-life of 36 months at 2°C - 8°C, where the finished product may be kept at or below 30°C for a single period up to 12 months or at or below 40°C for a single period up to 3 months for the new additional 4000 IU and 5000 IU strengths (for the unopened vial (before reconstitution). This shelf-life claim is identical to the shelf-life of the approved 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU strengths. In

addition, the MAH states that the in-use stability studies support a storage period of 24 hours at 2°C - 8°C or 4 hours at maximum 30°C for the reconstituted finished product (4000 IU and 5000 IU strengths).

PPQ finished product batches – 4000 IU and 5000 IU lots - have been put on stability. The stability study design includes evaluation of various storage conditions.

Stability data from process performance qualification (PPQ) batches (500 IU – 3000 IU) are included for comparison.

The present stability study includes data up to 6 months from 4000 IU and 5000 IU batches. The report covers results from the long-term and accelerated study. The stability study covers those attributes from the finished product specification that are susceptible to change during storage and which are likely to influence quality, safety and/or efficacy of turoctocog alfa pegol finished product.

The available stability results from the 4000 IU and 5000 IU lots have been compared with the stability data from process performance qualification batches (500 IU – 3000 IU). This comparison indicates that the stability behaviour of the 4000 IU and 5000 IU lots is consistent with the currently documented trends observed for PPQ stability batches (500 IU – 3000 IU).

Taking these arguments into account, the proposed shelf-life for the 4000 IU and 5000 IU can be agreed. Nonetheless, the MAH is recommended to continue and finalise the ongoing stability studies with the 4000 IU and 5000 IU lots according to the study design described and to notify the authorities in case of confirmed OOS during the long-term storage condition (Recommendation 1).

2.3.3.5. Adventitious agents

There are no changes to this section.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The MAH submitted a line extension of the marketing authorisation for Esperoct with the scope of introducing two new strengths (4000 IU and 5000 IU). The changes in the quality part are related primarily to the finished product as only the amount of active substance is changing, while the excipients amount is the same as for the marketed strengths of Esperoct.

There is no change affecting the active substance (turoctocog alfa pegol) and it is the same active substance as the already marketed strengths of Esperoct. Moreover, for the new strengths the device component, the container closure system (besides the cap colour) and the reconstitution diluent in a prefilled syringe remain the same as approved for the marketed strengths of Esperoct.

The development of the additional 4000 IU and 5000 IU strengths have been appropriately addressed; questions addressing the comparability evaluation (approved versus proposed additional strengths) as well as the compatibility studies of reconstituted finished product in contact with the vial adapter and in contact with the syringe for administration have been satisfactorily solved.

The finished product manufacturing process remains essentially unchanged except that the sampling strategy for quality control is changed and that the bioburden limits are changed. In addition, a few editorial changes were made in this section. The turoctocog alfa pegol manufacturing process is already validated for the 500 IU - 3000 IU strengths in a batch size range. A full-scale manufacturing validation has been performed for

the manufacturing process of turoctocog alfa pegol finished product with the two new strengths of 4000 IU and 5000 IU in the manufacturing facility licensed for commercial production.

The full–scale manufacturing validation of 4000 IU - 5000 IU is supplemental to the existing validation resulting in a validation product range of 500 - 5000 IU in a batch size range based on identical manufacturing process and product sameness. The MAH's conclusion that the consecutive validation batches demonstrated a high level of process reproducibility and consistency both in terms of the routine process controls and the analytical results of the supplementary sampling programme can be agreed. No changes in the specifications have been implemented except the updates with the new strengths. These updates for the 4000 IU and 5000 IU include strength-specific specification limits. These limits are based on the specification limits for the existing strengths and can be agreed on.

The analytical procedures are unchanged as approved for the marketed strengths and have been validated for the new strengths. Supplementary validation was performed.

Appropriate documentation of the conducted nitrosamine risk assessment has been included in the dossier. No risk of presence of nitrosamines in the active substance and finished product has been identified.

In summary a well-established and appropriately updated Module 2 and 3 for the new additional finished product strengths has been submitted. From a quality perspective the new 4000 IU and 5000 IU strengths of Esperoct are approvable.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of these two new strengths (4000 IU and 5000 IU) is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The MAH is recommended to continue and finalise the ongoing stability studies with the 4000 IU and 5000 IU lots according to the study design described and to notify the authorities in case of confirmed OOS during the long-term storage condition.

2.4. Non-clinical aspects

2.4.1. Introduction

This Line Extension concerns the introduction of new strengths (4000 and 5000 IU) and the change is related solely to the drug product as only the amount of drug substance is changing, while the excipients amount is the same as for the marketed strengths of Esperoct.

There is no change affecting the drug substance (turoctocog alfa pegol) and it is the same drug substance as the already marketed strengths of Esperoct. Moreover, for new strengths (4000 and 5000 IU) the drug product manufacturing process, the analytical procedures (validated), the device component and the

container closure system (besides the cap colour) remain the same as approved for the marketed strengths of Esperoct.

2.4.2. Pharmacology

Not applicable.

2.4.3. Pharmacokinetics

Not applicable.

2.4.4. Toxicology

2.4.4.1. Tolerance

The proposed new strengths of 4000 and 5000 IU will result in concentrations of 1000 IU and 1250 IU/mL turoctocog alfa pegol, respectively. Local tolerance studies submitted for the initial marketing authorization include only concentrations of up to 500 IU/mL. In order to justify that the administered concentrations of 1000 and 1250 IU/mL resulting from the proposed new strengths (4000 and 5000 IU) are covered by non-clinical studies, the MAH referred to a single dose toxicity study that was submitted in the scope of the initial MAA dossier.

In the single dose toxicity study 212344, rats received single i.v. administrations of 20000 and 25000 IU/kg at a concentration of 2000 IU/mL via the tail vein and no adverse reactions were observed. This corresponds to four times the concentration that was applied in the actual local tolerance study, which in addition included perivenous and intraarterial administration (all into the ear). The local reactions seen in these rats across all dose groups including controls were considered related to the intravenous administration. Although not exactly following recommendations for local tolerance studies the results of study 212344 are regarded sufficient in addition to the dedicated local tolerance study to cover the safety of the new intended clinical concentrations of 1000 and 1250 IU/mL.

Upon request of one authority, a new local tolerance study with the highest concentration of 1250 IU/mL was conducted in New Zealand White Rabbits. The study report was not completed at the time of response submission, however, according to the MAH's preliminary statement, no difference to control injection sites was observed.

2.4.5. Ecotoxicity/environmental risk assessment

According to EMA guideline "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. Turoctocog alfa pegol is a biological product consisting of a protein (rFVIII), coupled to polyethylene glycol (40 kDa) via a chemical linker (cytidin-5'-sialic acid-glycyl). The active pharmaceutical ingredient, rFVIII, and the chemical linker are due to their composition expected to be readily biodegradable.

Polyethylene glycol (40 kDa) is not expected to be readily biodegradable but it is not hazard labelled according to the EU legislation and it has no known adverse effects to the environment.

Thus, the proposed line extension for the new strengths of 4000 IU and 5000 IU is not expected to change the risk posed to the environment by Esperoct.

2.4.6. Discussion on non-clinical aspects

The MAH did not submit additional non-clinical studies in support of the new strengths of 4000 IU and 5000 IU turoctocog alfa pegol, which is in principal acceptable. A justification for the coverage of local tolerability of the resulting new concentrations, i.e. 1000 and 1250 IU/mL turoctocog alfa pegol, by existing studies was provided and is considered acceptable. In addition, a new local tolerance study was conducted in New Zealand White Rabbits for which the final study report was not available at the time of submission of the results, however, no adverse reactions were reported.

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, turoctocog alfa pegol is not expected to change the risk posed to the environment.

2.4.7. Conclusion on the non-clinical aspects

No concerns are raised on the addition of the two new strengths on a non-clinical perspective.

2.5. Clinical aspects

No new clinical data were submitted by the MAH to support this line extension, which intends to introduce vials containing 4,000 IU and 5,000 IU of turoctocog alfa pegol to the available palette of vials with 500 IU, 1,000 IU, 1,500 IU, 2,000 IU and 3,000 IU. While the amount of protein is increased in the new drug products, the amount of excipients remains unchanged.

In the clinical trial programme, only vials with 500 IU and 2,000 IU strength were investigated.

The Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2) states that: If a factor VIII product should be marketed in different strengths leading to a broad range of factor VIII concentrations after reconstitution, the pharmacokinetics of the lowest and highest concentration should be investigated unless otherwise justified.

The MAH was asked to justify that, even though the protein content in the highest strength vials is 10 times that of the lowest strength while the excipient content is identical, there is no clinically relevant concern regarding adsorption of the protein to the surfaces of the syringe and the tubing of the butterfly needle during preparation and administration of Esperoct. The MAH justified that a different behaviour of the protein solutions at the higher concentration is not expected. Consequently, the concern outlined was considered solved.

2.6. Risk Management Plan

Not applicable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. 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.

2.8. 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 for the following reasons:

The MAH refers to the positively tested user consultation results of the approved Esperoct presentations in February 2018. Only minor deviations from the already approved presentations were included.

3. Benefit-Risk Balance

This Line Extension concerns the introduction of two new strengths (4000 IU and 5000 IU) of Esperoct.

The quality of the new strengths is considered acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

No new non-clinical and clinical data have been provided which is considered acceptable.

Therefore, the benefit-risk is considered positive for the addition of 4000 IU and 5000 IU strengths.

3.1. Conclusions

The overall benefit/risk balance of Esperoct 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 Esperoct is not similar to 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 Esperoct 4000 IU and 5000 IU is favourable in the following indication:

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency). Refixia can be used for all age groups.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Esperoct 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 post-authorisation safety study according to an agreed protocol.	31/12/2027

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

Not applicable.