25 January 2018
EMA/CHMP/114079/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nuwiq

International non-proprietary name: simoctocog alfa

Procedure No. EMEA/H/C/002813/0000

Note

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

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List of abbreviations

DP = Drug Product

DS = Active substance

FPS = Final Product Specification

FVIII = factor VIII

FVIII:C = factor VIII activity

HPLC = High performance liquid chromatography

Human-cl rhFVIII = human cell line recombinant human factor VIII (Nuwiq)

IS = international standard

IU = international unit

LOQ = List of Questions

mL = milliliter

OOS = Out of specification

PV = process validation

RSD = relative standard deviation

SEC-HPLC = Size exclusion chromatography-high performance liquid chromatography

SDS-PAGE = Sodium dodecyl sulfate polyacrylamide gel electrophoresis

VWF = von Willebrand factor

1. Background information on the procedure

1.1. Submission of the dossier

Octapharma AB submitted on 27 April 2017 an extension of the marketing authorisation.

The MAH applied for a change or addition of a new strength/potency, strength of 2500 IU, 3000 IU, 4000 IU for Nuwiq, powder and solvent for solution for injection.

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(s) (c) - Extensions of marketing authorisations

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 received Scientific Advice from the CHMP on 19 November 2015. The Scientific Advice pertained to quality 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: N/A

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 27 April 2017.
- The procedure started on 18 May 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 15 August 2017.
- During the meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview

and Advice to CHMP.

- During the meeting on 14 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 12 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 14 November 2017.
- During the PRAC meeting on 30 November 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 3 January 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 January 2018.
- During the meeting on 25 January 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 of the marketing authorisation for Nuwiq.

2. Scientific discussion

2.1. Problem statement

In accordance with Commission Regulation (EC) No. 1085/2003, the Applicant submitted on 27 April 2017 an extension application to the European Medicines Agency (EMA) for the existing Marketing Authorisation for Nuwiq.

With this extension application the Applicant is seeking approval for the new strengths 2500 IU, 3000 IU and 4000 IU to the existing strengths (250 IU, 500 IU, 1000 IU, 2000 IU- Marketing authorisation numbers: EU/1/14/936/001-004).

The extension application is based on quality data and on nonclinical local tolerance data.

About the product

Nuwiq 250 IU/500 IU/1000 IU/2000 IU was approved in Europe via Centralised Procedure on 22 July 2014. The active substance of Nuwiq is simoctocog alfa (human coagulation factor VIII). Nuwiq is produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) 293F cells.

Nuwiq 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 or 4000 IU) of recombinant factor VIII per vial. 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.

Nuwiq is indicated for: “Treatment and prophylaxis of bleeding in patients with haemophilia (congenital factor VIII deficiency). Nuwiq can be used for all age groups.”

Type of Application and aspects on development

This is an application for a change of an existing marketing authorisation leading to an extension as referred to in ANNEX 1 of Regulation (EC) No. 1234, 2008 - Addition of a new strength.

2.2. Quality aspects

2.2.1. Introduction

Nuwiq 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, 2000 IU of recombinant factor VIII and is reconstituted with a single-dose solvent pre-filled syringe containing 2,5mL of sterile water for injections (WfI). With this line extension application the MAH 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 2.5mL of sterile water for injections.

2.2.2. Active Substance

General information

The active substance of Nuwiq 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/vial, 3000 IU/vial and 4000 IU/vial 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

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

Subsequently, the production process of Nuwiq 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)”. The Bio1/Bio1 DP SVP production process of Nuwiq was presented as a variation application and has been approved in March 2017.

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 Nuwiq strengths in Bio1 DP SVP.

In relation to pharmaceutical development compatibility of Nuwiq 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 Nuwiq new strengths with reconstitution and injection devices.

Manufacture of the product and process controls

The manufacturing process of Nuwiq 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.

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

Process validation

Process validation was performed for the pharmaceutical production of Nuwiq 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 Nuwiq 250, 500, 1000 and 2000 IU/vial.

Product specification

Specifications of Nuwiq 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 Nuwiq (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/vial to 4000 IU/vial are manufactured identically up to and including the active substance (AS) level.

The higher strength vials require the processing of higher Nuwiq concentrations during finished product manufacturing. As this process change may affect the biological activity profile of Nuwiq 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 Nuwiq 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, physico-chemical 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 Nuwiq 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 Nuwiq strengths regarding the impurity profile.

In conclusion, comparability data provided for the addition of the 3 higher Nuwiq 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 Nuwiq.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension application concerns the addition of three new strengths for Nuwiq (2500 IU, 3000 IU and 4000 IU per vial). 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

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

2.3. Non-clinical aspects

2.3.1. Introduction

This extension application concerns the introduction of new product strengths 2500 IU (1000 IU/ml), 3000 IU (1200 IU/ml) and 4000 IU (1600 IU/ml) in addition to the currently approved strengths. The extension application is based on quality data and on non-clinical local tolerance data.

The non-clinical data package comprising 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 a new local tolerance study was performed as part of this application.

2.3.2. Toxicology

Local tolerance

A local tolerance study of Drug Product following a single perivenous administration in rabbits was performed as follows:

***Local tolerance study of four Nuwiq strengths following a single perivenous administration in rabbits*)**

96 hours after administration all animals were sacrificed and tissue samples of the injection sites were examined macroscopically and then collected and prepared for microscopic examination.

Macroscopic inspection of the application sites did not reveal any changes. Furthermore, the histomorphological examination of 16 ear localizations of rabbits did not reveal any morphological changes in the perivascular region of the ear which are considered to be test item-related. The haemorrhages and the minimal inflammatory reactions were regarded to be caused by the technical procedure. Signs of systemic toxicity did not occur.

2.3.3. Discussion on non-clinical aspects

Considering the result of the new local tolerance study performed as bridging study to assess the local tolerance of the new vial strengths of Nuwiq, 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 Nuwiq product strengths tested were well tolerated and did not reveal any test item-related changes at the injection site.

2.3.4. Conclusion on the non-clinical aspects

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 Nuwiq.

2.4. Clinical aspects

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 a local tolerance study. This is considered acceptable.

Additionally, the applicant proposes to collect clinical data on the new Nuwiq product strengths within the frame of the non-interventional GENA-99 post-authorisation study.

2.4.1. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. 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 Interventional clinical study (category 3)	Investigate immunogenicity, efficacy and safety of Human-cl rhFVIII 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 - Medication error including safety in home therapy setting - Safety in children	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.

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)
		< 2 years		
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

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
Cardiovascular events	Mentioned in the SmPC (section 4.4)	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) Mentioned in the PIL (Section 3)	None
Safety in previously untreated patients	Mentioned in the SmPC (Section 4.2 and 4.8)	None
Children < 2 years	Mentioned in the SmPC (Sections 4.2, 4.4 and 4.8)	None
Safety in pregnant or breast feeding women	Mentioned in the SmPC (Section 4.6)	None
Immune tolerance induction (ITI)	Mentioned in the SmPC (Section 4.4)	None

Conclusion

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

2.6. 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.

2.7. Product information

2.7.1. 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.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nuwiq (simoctocog alfa) is included in the additional monitoring list.

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

The manufacture of Nuwiq 2500 IU/vial, 3000 IU/vial and 4000 IU/vial has been sufficiently validated and finished product quality attributes for the new strengths have been found comparable to those of the other strengths.

The additional non-clinical data, submitted with this application, are considered to be adequate to support the comparability of the different strengths of Nuwiq.

The MAH proposes to collect clinical data on the new Nuwiq product strengths within the frame of the non-interventional GENA-99 post-authorisation study.

Based on the available information the Benefit/Risk Balance of Nuwiq remains unchanged.

3.1. Conclusions

The overall Benefit-Risk of Nuwiq is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the risk-benefit balance of the new strengths Nuwiq 2500 IU (1000 IU/ml), 3000 IU (1200 IU/ml) and 4000 IU (1600 IU/ml) is favourable in the following indication:

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

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

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

Not applicable.