PART VI
Summary of Activities in the Risk Management Plan by Product

Active substance:	Recombinant human coagulation FVIII (octocog alfa)

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	26 AUG 2020

Version number of RMP when this module was last updated	3.1

List of Abbreviations

AE	Adverse event
ED	Exposure day
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUHASS	European Haemophilia Safety Surveillance
FVIII	Factor VIII
LPLV	Last patient last visit
MAH	Marketing authorisation holder
MTP	Minimally treated patient
PBRER	Periodic benefit-risk evaluation report
PUP	Previously untreated patient
PV	Pharmacovigilance
PWH	Patients with haemophilia
RMP	Risk management plan
SPC	Summary of product characteristics

1. Summary of Risk Management Plan for Kovaltry®

This is a summary of the risk management plan (RMP) for Kovaltry®. The RMP details important risks of Kovaltry®, how these risks can be minimised, how more information will be obtained about risks and uncertainties (missing information), and how gaps in knowledge about the safety of Kovaltry® in certain groups of patients (missing information) will be filled.

The summary of product characteristics (SPC) for Kovaltry®and the package leaflet give essential information to healthcare professionals and patients on how Kovaltry® should be used.

This summary of the RMP for Kovaltry® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the RMP for Kovaltry®.

2. The Medicine and What it is Used For

Kovaltry® is authorised for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry® can be used for all age groups (see SPC for the full indication). It contains recombinant human coagulation FVIII (octocog alfa) as the active substance and it is given by injection.

Further information about the evaluation of the benefits of Kovaltry®can be found in the EPAR, including a plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/medicines/human/EPAR/kovaltry

3. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Kovaltry®, together with measures to minimise these risks and the proposed studies for learning more about Kovaltry® risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic benefit-risk evaluation report (PBRER) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Kovaltry® is not yet available, it is listed under 'missing information' below.

3.1 List of Important Risks and Missing Information

Important risks of Kovaltry® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kovaltry®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product in certain groups of patients is not yet available that is currently missing.

Table 3-1: List of important risks and missing information

Important identified risks	• Development of factor VIII inhibitors • Hypersensitivity and allergic reactions
Important potential risks	• Cardiovascular/ thrombogenic events • Medication error/ product strength confusion
Missing information	• Risks in women, including pregnant and breast-feeding women

3.2 Summary of Important Risks and Missing Information

Important identified risk: Development of Factor VIII (FVIII) inhibitors	
Evidence for linking the risk to the medicine	• Study 12954 • Study 12954 Part B extension • Study 14319 • Study 13400 (Part A and Part B)
Risk factors and risk groups	The reasons why about one third of previously untreated patients (PUPs) develop inhibitors and the other two thirds are seemingly tolerant to the foreign FVIII protein still continues to be investigated (1, 11). What is known so far is that inhibitor development is a result of an intricate interplay of both genetic and environmental factors, with the causal *F8* gene mutation and other polymorphisms in immune response genes playing a major role in this field (12-14). Numerous trials have analysed the correlation of factors with the risk of inhibitors. The most compelling patient-related factors are haemophilia severity, *F8* gene mutations, and other genetic factors such as family history of inhibitors, and race or ethnicity. The risk of developing an inhibitor is highest in the first 20 exposure days (EDs) to FVIII products, with > 95% inhibitors detected by the 50th ED. Inhibitor development is lowest in patients who have received FVIII products for more than 150 EDs (15). In the completed main phase of the clinical trial in PUPs/ minimally treated patients (MTPs), FVIII inhibitors were observed in 54.8% of patients. The inhibitor incidence might have been influenced by consecutive high titre inhibitor cases observed in the middle of the study. While the most recent cumulative data from the registries show that the inhibitor rate for Kovaltry® is in line with the expected range in PUPs, the data are limited due to low sample size.
Risk minimisation measures	Routine risk communication for informed decision-making • SPC sections 4.4 and 4.8 Routine risk communication recommending specific clinical measures to address the risk • SPC section 4.4 where recommendations on inhibitor testing/ treatment alternatives are provided Other routine risk minimisation measures beyond the Product Information • Prescription-only medicine • Treatment should be under the supervision of a physician experienced in the treatment of haemophilia
Additional pharmacovigilance activities	• Study 14149 • Study 15689

KOVALTRY®
(Recombinant human coagulation FVIII [octocog alfa])
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Important identified risk: Hypersensitivity and allergic reactions	
Evidence for linking the risk to the medicine	• Study 12954 • Study 12954 Part B extension • Study 14319 • Study 13400 (Part A and Part B)
Risk factors and risk groups	Until now, no risk groups have been identified.
Risk minimisation measures	Routine risk communication for informed decision-making • SPC sections 4.3, 4.4, and 4.8 Routine risk communication recommending specific clinical measures to address the risk • SPC section 4.4: Advice that if hypersensitivity symptoms occur, patients should discontinue the use of the product immediately and contact their physician. Recommendation that if shock occurs, standard medical treatment for shock should be implemented. Other routine risk minimisation measures beyond the Product Information • Prescription-only medicine • Treatment should be under the supervision of a physician experienced in the treatment of haemophilia
Additional pharmacovigilance activities	• Study 13400 extension • Study 14149

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Important potential risk: Cardiovascular/ thrombogenic events	
Data source	• Study 12954 • Study 12954 Part B extension • Study 14319 • Study 13400 (Part A and Part B)
Risk factors and risk groups	Studies of patients with haemophilia (PWH) found that patients with concomitant heart disease were likely to be older and more likely to have hypertension, hyperlipidaemia and diabetes than those without heart disease. Hypertension was found to be more common in PWH patients than in the general population. Additional factors associated with haemophilia, may increase the risk of cardiovascular disease.
Risk minimisation measures	Routine risk communication for informed decision-making • SPC section 4.4 Special warnings and precautions for use Routine risk communication recommending specific clinical measures to address the risk • SPC section 4.4 Special warnings and precautions for use: Patients should be evaluated for cardiac risk factors Other routine risk minimisation measures beyond the Product Information • Prescription-only medicine • Treatment should be under the supervision of a physician experienced in the treatment of haemophilia
Additional pharmacovigilance activities	• Study 14149

Important potential risk: Medication error/ product strength confusion	
Data source	• Study 12954 • Study 12954 Part B extension • Study 14319 • Study 13400 (Part A and Part B)
Risk factors and risk groups	Until now, no risk groups have been identified
Risk minimisation measures	Routine risk communication for informed decision-making • SPC section 2 Routine risk communication recommending specific clinical measures to address the risk • None Other routine risk minimisation measures beyond the Product Information • Prescription-only medicine • Treatment should be under the supervision of a physician experienced in the treatment of haemophilia • The amount of factor VIII in a vial ensures that the product is used correctly

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Missing information: Risks in women, including pregnant and breast-feeding women	
Risk minimisation measures	Routine risk communication for informed decision-making • SPC section 4.6 Routine risk communication recommending specific clinical measures to address the risk • None Other routine risk minimisation measures beyond the Product Information • Prescription-only medicine • Treatment should be under the supervision of a physician experienced in the treatment of haemophilia

3.3 Post-authorisation Development Plan

Table 3-2: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
13400: Leopold Kids extension (clinical trial) Ongoing	Investigation of long-term treatment with Kovaltry (at least 100 EDs)	• Development of FVIII inhibitors • Hypersensitivity and allergic reactions	LPLV estimated for Study 13400	2022
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 – Required additional pharmacovigilance activities				
14149: Evaluation of cases with AEs of special interest in the EUHASS registry (epidemiological study) Ongoing	The primary objectives are: • to establish a PV programme to monitor the safety of treatments for patients with haemophilia • to develop and maintain a database of haemophilia centres in Europe • to establish a Rapid Alert System for immediate Europe-wide notification of professionals treating patients with haemophilia, in case of unexpected or serious AEs	• Development of FVIII inhibitors • Hypersensitivity and allergic reactions • Cardiovascular/ thrombogenic events	An update will be provided with each PBRER and as soon as new interim or final results are available to the MAH	N/A
15689: Evaluation of AEs of special interest in the PedNet registry (epidemiological study)	The PedNet registry includes patients with severe (<1%), moderate (1–5%) and mild (5–25%) haemophilia A and B. The registry documents the patient history and treatment	• Development of FVIII inhibitors	An update will be provided with each PBRER and as soon as new interim or final results	PedNet registry planned to study cohort until 2020

Table 3-2: Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	data and safety data from diagnosis onwards, with all data collected in a standardised format		are available to the MAH	

AE: adverse event; ED = exposure day; EUHASS: European Haemophilia Safety Surveillance; FVIII: factor VIII; LPLV: last patient last visit; MAH: marketing authorisation holder; PBRER: periodic benefit-risk evaluation report; PV = pharmacovigilance