Summary of the Risk Management Plan for Jivi®

Active substance: Damoctocog Alfa Pegol

Version number: version 3.0

Document date: 13-October-2021

Based on the EU-RMP v2.1 dated 17-June-2021 for Jivi®

Jivi®
(Damoctocog Alfa Pegol)
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Jivi® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Jivi® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Jivi®, hereinafter referred to as Jivi®.

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1. Summary of Risk Management Plan (RMP) for Jivi®

This is a summary of the risk management plan (RMP) for Jivi®. The RMP details important risks of Jivi®, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).

The summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jivi® should be used.

This summary of the RMP 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 Jivi®.

2. Jivi® and What it is used for

Jivi® is authorised for indicated for the treatment and prophylaxis of bleeding in in previously treated patients (PTPs) aged ≥ 12 years with haemophilia A (congenital FVIII deficiency) (see SmPC for the full indication). It contains damoctocog alfa pegol as the active substance and it is given by injection.

Further information about the evaluation of Jivi®'s benefits can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Jivi®, together with measures to minimise such risks and the proposed studies for learning more about Jivi®'s 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 SmPC 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 the case of Jivi®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR 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 Jivi® is not yet available, it is listed under 'missing information' below.

3.1 List of Important Risks and Missing Information

Important risks of Jivi® 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 Jivi®. 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 that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

3.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	Development of Factor VIII inhibitors Hypersensitivity reactions Loss of efficacy associated with anti-polyethylene glycol (PEG) antibodies
Important potential risks	Off-label use Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs Thromboembolic events
Missing information	Use in patients with severe hepatic impairment Use in patients with renal insufficiency Use in elderly patients > 65 years of age Safety profile in women including pregnancy and lactation

3.2 Summary of Important Risks

Important identified risk: Development of Factor VIII inhibitors	
Evidence for linking the risk to the medicine	The development of antibodies to FVIII with neutralising properties (known as FVIII inhibitors) may have a great impact on treatment of patients with haemophilia. Therefore, inhibitor development is considered a medically significant event, and it is regarded as the most serious complication of FVIII replacement in patients with haemophilia.
Risk factors and risk groups	Widely accepted risk factors for inhibitor development to FVIII are the severity of the FVIII gene defect, the prior number of exposure days, haemophilia severity, ethnicity, genotype, inhibitor testing frequency, intensity of treatment and familial predisposition. Other risk factors are still under debate, such as the specific treatment regimen, age at first exposure, mode of administration, surgery, type of FVIII concentrate, concomitant vaccinations and extravasations during injection.
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Routine pharmacovigilance	Collection of adverse events of Factor VIII inhibition through: • Targeted post-marketing questionnaire on loss of drug efficacy that includes information pertaining to FVIII inhibitors.
Additional pharmacovigilance activities	• Interventional post-marketing study* to assess safety and efficacy of Jivi® (study 19764) • EUHASS registry (study 14149) • Multinational PASS (study 20904) *To meet requirements per Annex II for recombinant FVIII products of 200 previously treated patients for a total of 100 EDs.

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Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions have been observed in the clinical trial program. These events are usually mild to moderate in intensity and resolve rapidly upon discontinuation of drug administration.
Risk factors and risk groups	Hypersensitivity reactions have been observed with the first four infusions primarily in patients < 6 years of age. Hypersensitivity may also be related to an immune response to polyethylene glycol. In patients ≥12 years the incidence of hypersensitivity reactions associated with anti-PEG antibodies was 0.7% (95% confidence interval [CI] 0-2.0%).
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Routine pharmacovigilance	Collection of adverse events of hypersensitivity reactions through: • Targeted post-marketing questionnaire on hypersensitivity reactions.
Additional pharmacovigilance activities	• Interventional post-marketing study* to assess safety and efficacy of Jivi® (study 19764) • Multinational PASS (study 20904) *To meet requirements per Annex II for recombinant FVIII products of 200 previously treated patients for a total of 100EDs.

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Important identified risk: Loss of efficacy associated with anti- polyethylene glycol (PEG) antibodies	
Evidence for linking the risk to the medicine	Loss of efficacy associated with development of anti-polyethylene glycol antibodies has been identified in clinical trials.
Risk factors and risk groups	The risk was only seen in patients 6 years of age and younger. Loss of efficacy associated with development of anti-PEG antibodies has been identified in clinical trials following administration of the 2nd to 4th dose, with no additional cases observed at a later time point.
Risk minimisation measures	**Routine risk minimisation measures** • "Age restriction" • Information provided to healthcare professionals and patients in the existing labelling materials
Routine pharmacovigilance	Collection of adverse events of Loss of drug efficacy associated with anti- polyethylene glycol (PEG) antibodies through: • Targeted post-marketing questionnaires on loss of efficacy
Additional pharmacovigilance activities	• Interventional post-marketing study* to assess safety and efficacy of Jivi® (study 19764) • Multinational PASS (study 20904) *To meet requirements per Annex II for recombinant FVIII products of 200 previously treated patients for a total of 100EDs.

Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	Age < 6 years has been determined during the clinical trials to be a risk factor for development of anti-PEG Immunoglobulin M antibodies following exposure to Jivi®. Development of these antibodies is associated with the clinical events of loss of efficacy / hypersensitivity. In order to minimize the risk of these events, the population has been restricted to Haemophilia A patients age ≥ 12 years.

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Risk factors and risk groups	Age < 12 years
Risk minimisation measures	**Routine risk minimisation measures** Collection of cases of off-label use.

Important potential risk: Long-term potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs.	
Evidence for linking the risk to the medicine	Accumulation of PEG in the choroid plexus has been demonstrated in non-clinical studies of other products at much higher doses of PEG than with Jivi®. There is no evidence from the non-clinical studies with Jivi® or from the PEG plasma level at steady state for clinically relevant accumulation of PEG in tissues.
Risk factors and risk groups	Very young patients could potentially be more impacted by high levels of PEG.
Risk minimisation measures	Information provided to healthcare professionals in the labelling materials is proposed.
Routine pharmacovigilance	• Targeted post-marketing questionnaires on the development of renal impairment during Jivi treatment and on neurocognitive disorders.
Additional pharmacovigilance activities	• Interventional post-marketing study* to assess safety and efficacy of Jivi® (study 19764) • Multinational PASS (study 20904) • EUHASS registry (study 14149) *To meet requirements per Annex II for recombinant FVIII products of 200 PTPs for a total of 100EDs.

Important Potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	No cases reported in the clinical program.

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Risk factors and risk groups	Patients with existing cardiovascular risk factors have the potential for thromboembolic events when FVIII levels are normalized.
Risk minimisation measures	Information provided to healthcare professionals and patients in the existing labelling materials

Missing information: Use in patients with severe hepatic impairment	
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	• EUHASS registry (study 14149)

Missing information: Use in patients with renal insufficiency	
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	• EUHASS registry (study 14149)

Missing information: Use in elderly patients > 65 years of age	
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	None

Missing information: Safety profile in women including pregnancy and lactation	
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.

Missing information: Safety profile in women including pregnancy and lactation	
Additional pharmacovigilance activities	None

4. Post-authorisation Development Plan

4.1 Studies which are conditions of the Marketing Authorisation

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				
Multinational PASS Study 20904	To provide long-term safety data to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs.	Potential long term PEG-related adverse reactions	First patient visit Study completion by Study report by	Q2/2021 Q2/2028 Q4/2028
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				

4.2 Other Studies in Post-authorisation Development Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Interventional post-marketing study to assess safety and efficacy of Jivi® *Data from study 19764 together with data from the extensions to studies 13024 and 15912 will be pooled to meet	A post-marketing interventional study is required to fulfill EMA guidelines regarding the requirements for applications of marketing authorisation for recombinant or plasma-derived Factor VIII products.	Development of Factor VIII inhibitors Hypersensitivity Clinical response characterised by loss of efficacy associated with	Final report	2023

Summary of activities in the risk management plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
the requirement of 200 patients with at least 100 EDs.		anti-PEG antibodies		
Epidemiological study	EUHASS registry (study 14149) The EUHASS registry is an investigator-driven registry that is funded by the EU in addition to Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective Haemophilia Safety Surveillance System for Europe. Participating centres have agreed to report all relevant AEs in their patients in a prospective manner. Events that should be reported are: new inhibitors, infections, allergic reactions, thromboses, new malignancies and deaths.	Development of Factor VIII inhibitors Hypersensitivity reactions Potential long term PEG-related adverse reactions Use in patients with renal insufficiency Use in patients with hepatic impairment	Enrolment of first patient receiving Jivi® Quarterly listings Annual report Final report	Q4 2018 – Q1 2019 One quarter following the end of the reporting period (Upon receipt from EUHASS) 1 year after the end of the reporting period (Upon receipt from EUHASS) 2024