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Summary of the risk management plan (RMP) for Iblias (octocog alfa)

This is a summary of the risk management plan (RMP) for Iblias, which details the measures to be taken in order to ensure that Iblias is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Iblias, which can be found on Iblias's EPAR page.

Overview of disease epidemiology

Iblias is used for the treatment and prevention of bleeding in patients of all ages with haemophilia A. Haemophilia A is a bleeding disorder that is caused by the lack of factor VIII, which is one of the proteins involved in the blood coagulation (clotting) process. Patients with haemophilia A are more prone to bleeding than normal and have prolonged bleeding which may include internal bleeding into joints, muscles and internal organs.

Haemophilia A is caused by a defective gene on the X chromosome. Men are usually more likely to be affected than women as men have only one X chromosome.

Haemophilia A can occur in all races and ethnic groups. In approximately two thirds of patients haemophilia A is inherited, whereas in the remaining cases the disease arises from spontaneous mutations (changes in the gene). Worldwide, it is estimated that one child in every 10,000 will be born with haemophilia A.

Summary of treatment benefits

Iblias contains the active substance octocog alfa which replaces missing human factor VIII. The effectiveness of Iblias in preventing and treating bleeding has been shown in a main study involving 62 patients aged 12 years or older with severe haemophilia A who were previously treated with other factor VIII products. The number of bleeds that occurred during Iblias treatment was calculated as 3.8 bleeds per year on average (mostly into joints). This compared with an average of 6.9 bleeds per year before Iblias treatment. Comparable results were seen in patients who continued to take the medicine after completion of the initial study.

About 70% of the bleeding events that occurred were managed with a single injection of Iblias, and about another 15% responded to a second injection; the response was considered good or excellent in around 80% of cases. In 12 patients who required major surgery during the study, control of blood loss was also rated as good or excellent by the patients' doctors.

A second study involved 51 children under 12 years of age previously treated with other factor VIII products, who also had 3.8 bleeds per year on average during treatment with Iblias (mostly related to injuries). Response to treatment was considered good or excellent in about 90% of cases.

Data from a supportive study also confirmed the benefits of preventative treatment with Iblias in reducing the number of bleeds.

Unknowns relating to treatment benefits

The clinical studies of Iblias did not include women, elderly patients or patients with mild or moderate haemophilia A. There is no evidence to suggest that Iblias would work differently in such patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Development of antibodies to the medicine that reduce the action of factor VIII (factor VIII inhibitors)	The formation of neutralising antibodies (inhibitors) to factor VIII by the immune system (the body's natural defences) is a known complication in the management of individuals with haemophilia A. If such inhibitors develop, the medicine may not work properly to control bleeding. The level of inhibitors is measured using a blood test. The risk of developing inhibitors is related to how much factor VIII has already been given and to genetic factors. It is highest within the first 20 days of exposure to (treatment with) factor VIII, although inhibitors may rarely develop after more than 100 days of exposure. Cases of recurrence of inhibitors have also been seen after switching from one factor VIII product to another in patients with a history of inhibitor development and more than 100 days of previous treatment.	Patients should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. In the presence of an inhibitor, the doses of Iblias must be adjusted by the doctor according to clinical response and monitoring of plasma factor VIII activity. Other forms of treatment may need to be considered in patients with high levels of inhibitors.
Hypersensitivity and allergic reactions	As with any protein product given into a vein, allergic-type hypersensitivity reactions are possible and in some cases may lead to more serious reactions such as shock. In the studies to license Iblias, allergic reactions were uncommon (seen in less than 1 patient in 100). During studies, no patient developed signs of clinically relevant reactions against the trace amounts of hamster protein present in the preparation. However, the possibility of allergic reactions to such constituents exists in	Patients should be made aware that the occurrence of chest tightness, dizziness (including when getting up from sitting or lying down), hives, itchy rash (urticaria), wheezing and feeling sick or faint can constitute an early warning for hypersensitivity and anaphylactic reactions. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately and the patient should contact their doctor. Shock and other symptoms should be treated appropriately.

Risk	What is known	Preventability
	certain predisposed patients.	

Important potential risks

Risk	What is known
Effects on heart and circulation due to blood clots (cardiovascular/ thrombogenic events)	Patients with haemophilia who also have risk factors for events such as heart attacks or stroke that can be triggered by blood clots obstructing the circulation are normally at lower risk of these because their blood is less likely to clot. However, because Iblias increases the blood's clotting ability to normal levels, treated patients potentially have their risk of such events increased to that of similar individuals without haemophilia. Consequently, patients should be evaluated for cardiovascular risk factors (for example, smoking, obesity, high blood pressure and diabetes).
Medication error/ product strength confusion	Iblias is available in five different doses. Although no medication errors were detected in the Iblias studies to license the medicine and measures to reduce the risk of an error have been undertaken (in the product information, labelling and packaging), the potential for error or confusion of product strengths cannot be completely ruled out.

Missing information

Risk	What is known
Risks in women, including pregnant and breast-feeding women	Because haemophilia A is rare in women, experience regarding the use of factor VIII products during pregnancy and breast-feeding is not available. Therefore, the medicine should only be used during pregnancy and breast-feeding if clearly indicated. There are no fertility data available. Since Iblias is a form of the natural human factor VIII protein, no adverse effects on fertility are expected.
Risks in patients with severely reduced liver function (severe hepatic impairment)	Patients with liver disorders such as hepatitis C infection and chronic hepatitis were included in the studies carried out with Iblias. However, patients with active liver disease (defined as liver enzymes more than 5 times the upper limit of normal levels [ULN] in patients aged up to 12 years, and medical history, liver enzymes more than 5 times the ULN, or presence of severe liver disease in patients aged 12–65 years) were excluded, and data for these patients are therefore not available.
Risks in previously untreated patients	Patients given factor VIII medicines are at increased risk of developing inhibitors in the first 20 days of treatment (see *Development of antibodies to the medicine that reduce the action of factor VIII*, above). The safety and efficacy of Iblias in previously untreated patients are under investigation in an ongoing clinical study.
Risks in elderly	Clinical studies did not include patients aged 65 years or more. However,

Risk	What is known
patients > 65 years of age	clinical experience with other factor VIII medicines has not identified differences between the elderly and younger patients. As with any patient receiving factor VIII, doses for an elderly patient should be adjusted individually.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Iblias can be found on Iblias's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
13400: Leopold Kids Part B	Investigation of the safety and efficacy of Iblias in previously untreated patients	Development of factor VIII inhibitors Hypersensitivity and allergic reactions Risks in previously untreated patients Efficacy in previously untreated patients	Ongoing	2018
13400: Leopold Kids extension	Investigation of long-term treatment with Iblias (at least 100 exposure days)	Development of factor VIII inhibitors Hypersensitivity and allergic reactions	Ongoing	2020

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		Efficacy of long-term treatment in children		
16817: Leopold IV	Investigation of the safety and efficacy of Iblias in children from China	Development of factor VIII inhibitors Hypersensitivity and allergic reactions Efficacy in children from China	Planned	2021
14149: Evaluation of cases with adverse events (AEs) of special interest in the EUHASS (European Haemophilia Safety Surveillance) registry	The primary objectives are: to establish a pharmacovigilance 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 factor VIII inhibitors Hypersensitivity and allergic reactions Cardiovascular/ thrombogenic events Risks in patients with severe hepatic impairment Risks in previously untreated patients Risks in elderly patients > 65 years of age	Planned	An update will be provided with each regular review of the medicine (periodic benefit-risk evaluation report, PBRER) and as soon as new interim or final results are available to the marketing authorisation holder
15689: Evaluation of adverse events of	The PedNet registry includes patients with severe (less	Development of factor VIII inhibitors	Planned	An update will be provided with each PBRER and as soon as new

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
special interest in the PedNet (Pediatric Network) registry	than1% of normal level of factor VIII), moderate (1–5%) and mild (5–25%) haemophilia A and B. The registry documents the patient history and treatment data from diagnosis onwards, with all data collected in a standardised format	Risks in previously untreated patients		interim or final results are available to the marketing authorisation holder

Studies which are a condition of the marketing authorisation

The Leopold Kids Part B and Leopold Kids extension studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 01-2016.