PART VI: SUMMARY OF ACTIVITIES IN THE RMP BY MEDICINAL PRODUCT

VI.1 Elements for Summary Tables in the EPAR

VI.1.1 Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Inhibitor formation Hypersensitivity
Important potential risks	Lack of effect Risk of medication error due to new presentation
Important missing information	Limited clinical data on use of ADVATE for immune tolerance induction (ITI) Risk of misapplication of ADVATE

VI.1.2 Table of On-Going and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Protocol No.	Study Title	Milestones/ Exposure	Milestones/ Calendar	Study Status
060902	AHEAD-Study: ADVATE (Octocog alfa) Hemophilia A Outcome Database	-First Subject Enrolled -Last Subject In -Last Subject Out -Completion of Final Report	Q2/2011 Q4/2015 Q4/2017 Q4/2019	Ongoing
061001	ADVATE Hemophilia An Outcome Database (AHEAD)	-First Subject Enrolled -Last Subject In -Last Subject Out -Completion of Final Report	Q2/2011 Q2/2013 Q3/2017 Q1/2021	Ongoing

VI.1.3 Summary of Post Authorization Efficacy Development Plan

Not applicable.

VI.1.4 Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Activities	Additional Minimization Activities
Inhibitor Formation	Section 4.4 of the SmPC: "The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrent inhibitor (low titer) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development.Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low	None proposed

	titre posing less of a risk of insufficient clinical response than high titre inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors." Section 4.8 of the SmPC "Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ADVATE. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted."	
Hypersensitivity	Section 4.3 of the SmPC Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to mouse or hamster proteins. Section 4.4 of the SmPC" Allergic-type	None proposed

	hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. The product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Due to the decrease in injection volume for ADVATE reconstituted in 2 ml sterilised water for injections, if hypersensitivity reactions occur there is less time to react by stopping the injection. Therefore, caution is advised during injection of ADVATE reconstituted in 2 ml sterilised water for injections, especially in children.”	
Lack of Effect	Section 4.4 of the SmPC : “The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to	None proposed

	factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.”	

	Section 4.8 of the SmPC "Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ADVATE. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted."	
Risk of medication error due to new presentation	None Patients receive proper training prior to receiving their first treatment of ADVATE 2ml for home use Packaging for Advate was developed to differentiate the 2 ml presentation from the 5 ml presentation so the potential for confusion is minimized. Outer carton: The 2 ml presentation features a purple background on the carton. sWFI vial label: the 2 ml sWFI features a label with white font on a purple background, compared to dark blue print on a white background in the 5 ml presentation.	None proposed
Limited clinical data on use of ADVATE for immune tolerance induction (ITI)	Section 5.1 of the approved SmPC: "Data on Immune Tolerance Induction (ITI) in patients with inhibitors have been collected. Within a sub-study of PUP-Study 060103, ITI-treatments in 11 PUPs were documented. Retrospective	None proposed

	chart review was done for 30 subjects on ITI (Study 060703) and collection of Registry data is on-going."	
Risk of misapplication of ADVATE	Section 4.4 of the SmPC: "For ADVATE reconstituted with 2 mL sterilised water for injections, misapplication (intra-arterially or paravenously) may lead to mild, short term injection site reactions, such as bruising and erythema."	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Haemophilia is a rare bleeding disorder in which the blood does not clot normally. People with haemophilia do not bleed any faster than normal, but they can bleed for a longer time. Their blood does not have enough clotting factor. Clotting factor is a protein in blood.

Bleeding may occur inside the body, especially in knees, ankles, and elbows. This bleeding can damage organs and tissues and may be life threatening.

People born with haemophilia have little or no clotting factor. Clotting factor is a protein needed for normal blood clotting. There are several types of clotting factors. These proteins work with platelets to help the blood clot.

Platelets are small blood cell fragments that form in the bone marrow—a sponge-like tissue in the bones. Platelets play a major role in blood clotting. When blood vessels are injured, clotting factors help platelets stick together to plug cuts and breaks on the vessels and stop bleeding.

Haemophilia is quite rare. About 1 in 10,000 people are born with it. Haemophilia usually is inherited. “Inherited” means that the disorder is passed from parents to children through genes.

Haemophilia usually occurs in males (with rare exceptions). About 1 in 5,000 males are born with haemophilia each year.

Haemophilia can be mild, moderate, or severe, depending on how much clotting factor is in the blood. About 7 out of 10 people who have hemophilia A have the severe form of the disorder.

Healthy people have a factor VIII activity of 100 percent. People who have severe haemophilia A have a factor VIII activity of less than 1 percent.

Inhibitors are a serious medical problem that can occur when the body forms antibodies (proteins) against clotting factors in the bloodstream. The antibodies can prevent the clotting factors from working.

VI.2.2 Summary of Treatment Benefits

Treatment with Replacement Therapy

The main treatment for haemophilia is called replacement therapy. Concentrates of clotting factor VIII (for haemophilia A) are slowly injected into a vein. These infusions help replace the clotting factor that's missing or low.

Clotting factor concentrates can be made from human blood. The blood is treated to prevent the spread of diseases, such as hepatitis. With the current methods of screening and treating donated blood, the risk of getting an infectious disease from human clotting factors is minimized. Other products like ADVATE are produced from cell lines and do not contain material from human blood.

Replacement therapy can occur on a regular basis to prevent bleeding. This is called preventive or prophylactic therapy. Replacement therapy may only be needed to stop bleeding when it occurs. This use of the treatment, on an as-needed basis, is called on-demand therapy.

On-demand therapy is less intensive and expensive than preventive therapy. However, there is a risk that bleeding will cause damage before the patient receives the on-demand therapy.

VI.2.3 Unknowns Relating to Treatment Benefits

ADVATE has been tested on many people in different age groups and of different races and ethnicities. Most of the people studied were Caucasian. Hispanic, Black, and Asian people were also studied. It is likely that ADVATE work well in people of all races and ethnicities. Also, many people have had good results with ADVATE.

Specific treatment methods for patients with existing antibodies are not clearly defined. With immune tolerance induction (ITI), ADVATE is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it. When ITI is successful, the inhibitors disappear and the patient’s response to ADVATE returns to normal. However, the best dose for eliminating inhibitors is unknown.

Due to the decrease in infusion volume for ADVATE reconstituted in 2 ml the time to react to hypersensitivity reactions during an infusion is further reduced. Caution is advised during injection of ADVATE reconstituted in 2 mL solvent, especially in children under 2.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Safety Concern in Lay Language (Medical term)	**Brief summary in lay language**	**Whether risk can be minimized or mitigated, and how**
Antibodies against factor VIII that reduce the efficacy of ADVATE to prevent or control bleeding. (Inhibitor formation)	Development of inhibitors is a known complication in the treatment of haemophilia A.	There is no documented method to prevent FVIII inhibitor formation. However, recent studies have suggested that the early use of prophylactic FVIII replacement may reduce the risk of inhibitor formation during early life.
Sudden allergic reactions (Hypersensitivity)	Potentially life-threatening reactions (anaphylaxis) and other allergic reactions (hypersensitivity) can occur	Patients are informed of the early signs of hypersensitivity reactions and advised to discontinue use of product if they develop these signs.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Reduced efficacy of ADVATE to prevent or control bleeding due to antibodies against factor VIII. (Lack of Effect)	Drug effect decreased/Lack of drug effect or complete drug ineffectiveness may be associated with inhibitor formation.
Risk of medication error due to new presentation	Risk of confusion between the 2 ml presentation and 5 ml presentation especially in home treatment settings while maintaining the currently approved packages with identical strengths.

Important Missing Information

Risk	What is known
Limited clinical data on use of	Recombinant Factor VIII products have been

Risk	What is known
ADVATE for immune tolerance induction (ITI) With immune tolerance induction (ITI) therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it. When immune tolerance induction is successful, the inhibitors disappear and the patient's response to factor concentrates returns to normal.	used off-label in a variety of therapeutic regimens, however, the overall safety and optimal dosing regimen of the rFVIII administration in ITI therapy remains inadequately defined.
Risk of misapplication of ADVATE	ADVATE is to be administered in the blood vessels after reconstitution of the lyophilized product with the provided sterilized water for injection. There is a risk of inadvertent infusion into the artery or outside the vein and mild, short term injection site reactions, such as bruising and redness may occur.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

There are no additional risk minimization measures for the safety concerns for ADVATE.

VI.2.6. Planned Post Authorization Development Plan

There are no planned post authorization studies for ADVATE.

Studies which are a Condition of the Marketing Authorization

None of the above studies are conditions of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 16. Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
1.0	21 June 2007 DLP 28 February 2007	Important Identified Risks: • Inhibitor formation	The formation of neutralizing antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with haemophilia A.
		Important Potential Risk: • None	
		Important Missing Information: • None	
2.0	06 December 2007 DLP: 28 July 2007 Upon request of EMA, a revised ADVATE RMP was submitted for the currently licensed strengths of ADVATE (250, 500, 1000, 1500 IU)	Important Identified Risks: • Inhibitor formation	
		Important Potential Risk: • None	
		Important Missing Information: • Rate of Inhibitor formation	The established incidence of inhibitor development was not yet published, due to a study that was ongoing. The safety concern Rate of Inhibitor formation was added as missing information.
3.0	31 March 2008 DLP: 28 Jun 2007 Upon request of	Important Identified Risks: • Inhibitor formation	
		Important Potential Risk: • None	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
	EMA, a revised ADVATE RMP was submitted for the extension application EMEA/H/C/520/X/ 23 for the 2000 IU and 3000 IU/vial potency strengths	Important Missing Information: • Rate of Inhibitor formation	
4.0	08 May 2008 DLP: 29 April 2008	Important Identified Risks: • Inhibitor formation Important Potential Risk: • None	
		Important Missing Information: • Rate of Inhibitor formation	
5.0	23 September 2008 DLP: 31 July 2008	Important Identified Risks: • Inhibitor formation	
		Important Potential Risk: • Hypersensitivity • Lack of effect	EMEA request to include both hypersensitivity and lack of effect as potential risk
		Important Missing Information: • Rate of Inhibitor formation	
6.0	26 February 2009 DLP: 21 January 2009	Important Identified Risks: • Inhibitor formation Important Potential Risk: • Hypersensitivity • Lack of Effect	
		Important Missing Information: • Rate of Inhibitor formation	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
7.0	30 September 2009 DLP: 31 July 2009	Important Identified Risks: • Inhibitor formation	
		Important Potential Risk: • Hypersensitivity • Lack of effect	
		Important Missing Information: • Rate of inhibitor formation	The mechanism and incidence of inhibitor development in PTP compared to PUP has not been published and the related study 060103 is on-going. Further, the experience concerning the inhibitor development in children has not been provided yet as the "PUP-Study" is ongoing.
8.0	01 April 2010 DLP: 31 January 2010	Important Identified Risks: • Inhibitor formation Important Potential Risk: • Hypersensitivity • Lack of effect	
		Important Missing Information: • Rate of inhibitor formation	
9.0	11 June 2010 DLP: 10 June 2010	Important Identified Risks: • Inhibitor formation • Hypersensitivity	Hypersensitivity moved from potential to identified risk
		Important Potential Risk: • Lack of effect	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		Important Missing Information: • Rate of inhibitor formation • Limited clinical data on use of ADVATE for immune tolerance induction (ITI)	Recombinant Factor VIII products have been used off-label in a variety of therapeutic regimens, however, the overall safety and optimal dosing regimen of the rFVIII administration in ITI therapy remains inadequately defined. Limited clinical data on use of ADVATE for immune tolerance induction (ITI) was added as important missing information.
10.0	16 March 2011 DLP: 01 March 2011	Important Identified Risks: • Inhibitor formation • Hypersensitivity	
		Important Potential Risk: • Lack of effect	
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI)	Rate of inhibitor formation was removed from missing information due to receipt of data from completed study.
11.0	29 September 2011 DLP: 21 September 2011	Important Identified Risks: • Inhibitor formation • Hypersensitivity	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
	This version was prepared in response to changes requested by the CHMP regarding the variation to update sections 4.2, 4.4 and 5.1 of the SmPC to include information on immune tolerance induction (EMEA/H/C/520/II /38) and to introduce ADVATE 2 mL (EMEA/H/C/530/X /41).	Important Potential Risk: • Lack of effect • Risk of medication error due to new presentation	The introduction of some additional reduced volume presentations while maintaining presentations with identical strengths (250, 500, 1000 and 1500 IU per vial) may lead to a potential risk of confusion especially in home-treatment-setting. Risk of medication error due to new presentation added as a potential risk.

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI) • Risk of misapplication of Advate • Lack of data in children <2 years old regarding the use of 2 ml presentation	There is a risk of inadvertent paravenous or intra-arterial application. In addition, due to the decrease in infusion volume for Advate reconstituted in 2 ml sWFI, the healthcare professional's time to react to hypersensitivity reactions during an infusion is reduced. Therefore, the Risk of misapplication of Advate and Lack of data in children <2 years old regarding the use of 2 ml presentation were added as important missing information
12.0	21 February 2012 DLP: 31 January 2012	Important Identified Risks: • Inhibitor formation • Hypersensitivity	
		Important Potential Risk: • Lack of effect • Risk of medication error due to new presentation	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI) • Risk of misapplication of Advate • Lack of data in children <2 years old regarding the use of 2 ml presentation	
13.0	22 October 2012 DLP: 08 October 2012	Important Identified Risks: • Inhibitor formation • Hypersensitivity	
		Important Potential Risk: • Lack of effect • Risk of medication error due to new presentation	
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI) • Risk of misapplication of Advate • Lack of data in children <2 years old regarding the use of 2 ml presentation	
14.0	02 April 2013 DLP: 31 January 2013	Important Identified Risks: • Inhibitor formation • Hypersensitivity	
		Important Potential Risk: • Lack of effect • Risk of medication error due to new presentation	

Table 16. Major Changes to the Risk Management Pla Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI) • Risk of misapplication of Advate • Lack of data in children <2 years old regarding the use of 2 ml presentation	
15.0	10 July 2013 DLP: 31 May 2013	Important Identified Risks: • Inhibitor formation • Hypersensitivity	
		Important Potential Risk: • Lack of effect • Risk of medication error due to new presentation	
		Important Missing Information: • Limited clinical data on use of ADVATE for immune tolerance induction (ITI) • Risk of misapplication of Advate • Lack of data in children <2 years old regarding the use of 2 ml presentation	
15.1	14 Dec 2017 DLP: 27 July 2017	Removal of Important Missing Information due to data received: • Lack of data in children <2 years old regarding the use of 2 ml presentation	