

## **VI.2 Elements for a Public Summary**

### ***VI.2.1 Overview of Disease Epidemiology***

Octanate is indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency), a sex-linked recessive trait with the defective gene located on the X chromosome.

In severe haemophilia A, the blood level of coagulation factor VIII is undetectable (< 1% of normal) whilst in moderate and mild forms, some factor VIII is detectable in the blood. If untreated, patients with severe deficiencies may have frequent spontaneous bleeding into joints and muscles. Certain joints seem to be particularly afflicted notably the knees, ankles, and elbows. Severely affected haemophiliacs also bleed excessively during minor surgery (e.g., tooth extraction) and may suffer life-threatening bleeding from traumatic or even relatively mild injury.

Moderately affected patients have factor VIII levels of between 1% and 5% of normal and only occasionally experience spontaneous bleeding, although traumatic bleeding is problematic. In mildly affected haemophiliacs, who have factor VIII levels of more than 10%, treatment is usually only required for traumatic bleeding.

Replacement of the missing factor VIII with Octanate corrects the bleeding problems in haemophilia A. Many severe haemophiliacs are treated at home, injecting themselves either prophylactically or when they experience a bleeding episode, the latter modality known as on-demand treatment.

The worldwide incidence of haemophilia A is about 1 case per 5000 male individuals. The prevalence of haemophilia A varies with the reporting country, with a range of 5.4–14.5 cases per 100,000 male individuals. The mortality rate of patients with haemophilia is twice that of the healthy male population; for severe haemophilia, it is 4–6 times higher [Error! Bookmark not defined.].

### ***VI.2.2 Summary of Treatment Benefits***

The comparison of the efficacy results across studies showed consistent efficacy. The mean recoveries of factor VIII determined at baseline, 3 months, and 6 months were within the expected range of 1.5% to 2% per IU/kg body weight (BW) or higher and remained consistent over time. Factor VIII consumption was within the expected range for the nature and severity of the bleeding episodes in all studies.

Haemostatic efficacy in the initial analysis of these studies was assessed for treatment of bleeding episodes, during surgeries, and for prophylactic treatment. Using a 4-point subjective scale, efficacy was assessed as ‘excellent’ or ‘good’ in a high percentage of cases, ranging from 84% in study AVI-407 to 100% in study AVI-408. Where no efficacy was observed for an Octanate infusion, treatment was generally continued, with a positive outcome documented after subsequent administrations. Efficacy in previously untreated patients (PUPs) was rated as excellent in 99.8% of the patients. Use of Octanate to cover surgical procedures was also shown to be effective, with good factor VIII recovery and haemostatic effect. Octanate consumption, blood loss, and transfusion requirements were all as expected for the types of procedure performed.

Using more stringent post-hoc criteria, the majority of bleeding episodes were assessed as successfully treated (94.3%) within adequately short time periods (95%). Studies with previously treated patients (PTPs) had a 92.7% success rate, while success rate in previously untreated patients (PUP)s was slightly higher at 96.9%. Thus, even when assessed using more stringent efficacy evaluation criteria, Octanate successfully treated bleeding episodes in a high proportion of patients.

Based on the data from the third interim analysis for the ObsITI observational study it may be concluded that Octanate, administered mainly according to the high-dose Bonn protocol, is effective in immune tolerance induction (ITI) according to pre-specified success criteria in patients with a poor prognosis for ITI success. In addition, the frequency of bleeding episodes (Bes) and the use of bypassing agents (BPAs) at the start of ITI were significantly reduced after inhibitor eradication.

Overall, based on the studies performed by Octapharma, published studies with other factor VIII products, and the experience on the international market, it can be concluded that Octanate is efficacious in the approved indications.

### ***VI.2.3 Unknowns Relating to Treatment Benefits***

Efficacy data in pregnant and breast feeding women are limited. There is no evidence to suggest that results would be any different in this population.

## VI.2.4 Summary of Safety Concerns

### Important identified risks

Risk	What is known	Preventability
<b>Inhibitor development in PUPs with haemophilia A</b>	According to the data from the scientific literature, inhibitor development has been associated with recombinant and plasma-derived factor VIII products and affects approximately 20% to 30% of previously untreated patients (PUPs) with severe haemophilia A after exposure to a factor VIII concentrate [Error! Bookmark not defined.]. Data obtained from the Octapharma-sponsored clinical trials and post-marketing sources indicates that the inhibitor rate is lower, see Section SVII.3. In previously treated patients (PTPs), the observed incidence of inhibitors is lower, ranging from 0.9% to 4.0% [Error! Bookmark not defined.,Error! Bookmark not defined.].	<ul style="list-style-type: none"> <li>• Patients should not be switched carelessly from one factor VIII concentrate to another.</li> <li>• Patients should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.               <ul style="list-style-type: none"> <li>○ Appropriate warning in the SmPC and product labelling.</li> </ul> </li> </ul>
<b>General tolerability (hypersensitivity and allergic reactions)</b>	May be serious (very rarely). Usually patients recover following treatment.  Risk factors include a history of hypersensitivity, immunoglobulin A (IgA) deficiency, presence of anti-IgA antibodies, previous severe systemic reactions to the administration of human plasma-derived products.	<ul style="list-style-type: none"> <li>• Premedication (antihistamines and intravenous hydrocortisone)</li> <li>• Assessment of individual patient risk</li> <li>• Slow infusion rates               <ul style="list-style-type: none"> <li>○ Appropriate warning in the SmPC and product labelling.</li> </ul> </li> </ul>

### Important potential risks

Risk	What is known
<b>Transmission of</b>	The solvent-detergent method is known for its effectiveness in

Risk	What is known
<b>viruses</b>	<p>inactivating lipid-enveloped viruses. Dry-heat treatment (100°C for 30 minutes) effectively inactivates enveloped as well as non-enveloped viruses. Further steps that possibly contribute to the viral safety are immune neutralisation, cryoprecipitation, adsorption on Al(OH)<sub>3</sub>, and ion exchange chromatography.</p> <p>The manufacturing measures implemented may be of limited value against non-enveloped viruses such as parvovirus B19 (B19).</p> <p>A theoretical consideration is the possible transmission of hitherto unknown viruses or of the causative agents of transmissible spongiform encephalopathy (TSE), in particular variant Creutzfeldt-Jakob Disease (vCJD).</p>

### Important missing information

None.

### *VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern*

No additional risk minimisation measures are necessary.

### *VI.2.6 Planned Post-authorisation Development Plan*

List of studies in post-authorisation development plan.

Study	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
AVI-403 Prospective, international, multicentre, open-label, non-controlled, phase III study	The primary objective of the study is to assess the immunogenicity of Octanate in PUPs by monitoring inhibitors against factor VIII (using the Bethesda assay with Nijmegen modification) every 3-4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, whichever comes first.	Incidence of inhibitors in PUPs with severe haemophilia A treated with Octanate.	Started	Study start: Feb-2000 First interim report: Q1 2008 Second interim report: Q3 2009 Final study report: 2014

NATE-02 Open-label, non-interventional, prospective, multi-centre, multinational, observational post-marketing study	The objective of this observation is to assess the clinical efficacy, tolerability, and immunogenicity of Octanate in patients with haemophilia A.	The aim of this study is to collect further information concerning the clinical efficacy, tolerability, and immunogenicity of Octanate.	Started	Study start: Q4 2009 First interim report: 2015 Final study report: 2017
ITI-01 Open-labelled, non-controlled post-marketing surveillance study	To evaluate the efficacy of Octanate or Wilate in eliminating inhibitors in haemophilia A patients using individualised immune tolerance induction (ITI).	Inhibitor elimination in haemophilia A patients.	Started	Study start: Q2 2012 First interim report: NA Final study report: 2016
ObsITI International open-label, uncontrolled, multi-centre observational program	To evaluate and document data on the success of ITI in haemophilia A patients with newly developed or already existing factor VIII-inhibitors (also patients who might potentially have failed in earlier ITIs), which will be treated with ITI - preferably high-dose based on individualized product selection.	Inhibitor elimination in haemophilia A patients.	Started	Study start: Jan-2006 First interim report: 30-Sep-2008 (Octanate) Second interim report: 30-Oct-2009 Third interim report: 13-Mar-2013 Final study report: NA

None of the above studies is a condition of the marketing authorisation.

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

<b>Version</b>	<b>Date</b>	<b>Safety Concerns</b>	<b>Comment</b>
01	30-Mar-2004	<b>Identified risks:</b> Inhibitor development in previously untreated patients (PUPs) with haemophilia A <b>Potential Risks:</b> None <b>Missing information:</b> None	First edition of RMP for Octanate.
02	21-Dec-2007	<b>Identified risks:</b> Inhibitor development in previously untreated patients (PUPs) with haemophilia A <b>Potential Risks:</b> Virus safety in general <b>Missing information:</b> None	None.
03	14-Jun-2013	<b>Identified risks:</b> 1. Inhibitor development in previously untreated patients (PUPs) with haemophilia A 2. Hypersensitivity and allergic reactions <b>Potential Risks:</b> Virus safety in general <b>Missing information:</b> None	Third edition of RMP for Octanate updated according to the Guidance on format of the risk management plan in the EU - GVP Module V.

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