LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Octanate LV
(human coagulation factor VIII)

SE/H/1070/03-04/DC

This module reflects the scientific discussion for the approval of Octanate LV. The procedure was finalised on 2014-10-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Octanate LV, 100 IU/ml and 200 IU/ml, powder and solvent for solution for injection, is an extension application made according to Article 8(3) of Directive 2001/83/EC, known active substance. The suffix “LV” refers to “low volume”. The active substance human coagulation factor VIII is the same as in Octanate, 50 IU/ml and 100 IU/ml, powder and solvent for solution for injection marketed by Octapharma AB since 2005. No Public Assessment Report is available for Octanate.
The applicant, Octapharma AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CY, CZ, DK, EL, ES, FI, FR, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI and UK as concerned member states (CMS).

The current presentations of Octanate, SE/H/1070/01-02 (up to 2011 AT/H/127/01/E01-02), are:

- 50 IU/ml (250 IU in 5 ml and 500 IU in 10 ml)
- 100 IU/ml (1000 IU in 10 ml)

With this line extension Octapharma is applying for the addition of alternative reconstitution volume of 5 ml solvent for Octanate 500 IU and 1000 IU, resulting in 100 IU/ml and 200IU/ml, see table below. This change does not affect the manufacturing process or physico-chemical properties before reconstitution. The freeze-dried powder remains unchanged.

	Octanate			**Octanate LV (low volume)**	
Pack size	1000 IU	500 IU	250 IU	1000 IU	500 IU
Volume solvent	10 ml	10 ml	5 ml	5 ml	5 ml
Strength	100 IU/ml	50 IU/ml	50 IU/ml	200 IU/ml	100 IU/ml
Excipient concentration after reconstitution	original			doubled	
Composition before reconstitution				Same as current Octanate 1000 IU	Same as current Octanate 500 IU

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Octanate LV is presented in the form of powder and solvent for solution for injection containing 100 IU per ml or 200 IU per ml, respectively, of human coagulation factor VIII when reconstituted with 5 ml of solvent. The excipients are sodium citrate, sodium chloride, calcium chloride and glycine. The powder and the solvent (water for injection) are filled in glass vials. The product is administered by intravenous injection.

II.2 Drug Substance

Factor VIII is isolated from human plasma. Regarding the quality of this starting material, the Plasma Master File (PMF) has been certified by EMA with the number EMEA/H/PMF/000008/05. The certified PMF covers the information about the measures put in place to prevent infections being passed on to patients from the starting material, such as careful selection of blood and plasma donors, testing of each donation and pools of plasma for signs of virus/infections. The documentation on the drug substance remains identical to the drug substance dossier of the currently licensed presentations of Octanate.

II.3 Medicinal Product

Octanate LV powder and solvent for injection is formulated using excipients described in the current Ph Eur. The manufacturing process has been sufficiently described and critical steps are identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are in compliance with the European Pharmacopoeia monograph for Human coagulation factor VIII and are considered appropriate to control the quality of the finished product in relation to its intended purpose.

The measures taken to prevent transmission of infections resulting from the use of human blood or plasma, including the viral reduction by the process, are in compliance with the current CHMP and ICH guidelines and are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19, a matter to be considered for certain risk groups (see further Section 4.4 of the SmPC). No new data was provided for this application but reference is given to the product supplied in the current presentations of Octanate using the same manufacturing process.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. Stability after reconstitution of 500 IU and 1000IU vials, each in 5 ml, has been acceptably shown.

No material used in the manufacturing of Octanate originates from animal species susceptible to TSE.

III. NON-CLINICAL ASPECTS

III.1 Results and Discussion on the non-clinical aspects

The impact of the higher concentration of impurities in the volume reduced formulation were analysed in a safety pharmacology study, a pharmacokinetic study and a local tolerance study. Similar to the original product no thrombogenic effect was seen with the reduced formulation and no significant differences in the pharmacokinetics or local tolerance between Octanate 1000 IU FVIII and the original product were neither seen. It should be noted that, since the freeze-dried powder remains unchanged, the total amounts of impurities and excipients received after administration of the volume reduced formulation remain the same as for the original product.

III.2 Ecotoxicity/environmental risk assessment

Factor VIII is a protein and is therefore unlikely to result in significant risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No new pharmacokinetic studies have been conducted and none are needed for this extension application. The only change compared to the already licensed Octanate formulation is a reduced reconstitution volume. The administered dose will remain the same and no differences in pharmacokinetics are expected.

IV.2 Pharmacodynamics

N/A.

IV.3 Clinical efficacy

No new data was submitted which is accepted for this application, where the only change compared to the already approved Octanate formulation is a reduced reconstitution volume.

IV.4 Clinical safety

No new data was submitted, which is accepted for this application. See also “Clinical efficacy”.

IV.5 Discussion on the clinical aspects

No new data to assess.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Octanate LV, 100 IU/ml, 200 IU/ml, powder and solvent for solution for injection is recommended for approval.

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. APPROVAL

The Decentralised procedure for Octanate LV, 100 IU/ml, 200 IU/ml, powder and solvent for solution for injection was successfully finalised on 2014-10-13.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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