Unit: Technical Assessment Unit

Public assessment report for biological products

(Octanine F 100 IU/ml)

Administrative information:

Trade name of the medicinal product:	Octanine F 100 IU/ml
INN (or common name) of the active substance(s):	Human Coagulation Factor IX 500 IU (100 IU/ml)
Manufacturer of the finished product	Octapharma Pharmazeutika Produktionsges m.b.H, Oberlaaerstraβe 235, 1100 Wien – Austria Alternative manufacturer: Octapharma S.A.S, 70-72 rue du Marèchal Foch, BP 33, 67380 Lingolsheim - France.
Marketing Authorization holder	Octapharma Pharmazeutika Produktionsges m.b.H, Oberlaaerstraβe 235, 1100 Wien - Austria
Applied Indication(s):	Treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency).
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for IV injection (100 IU/ml)
Route of administration	I.V injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

BW: Body weight
CHMP: Committee for Human Medicinal Products)
EMA: European Medicines Agency
FIX: Coagulation factor IX
ISTH: International Society for Thrombosis and Haemostasias
IU: International unit
IV: Intravenously
Kg: Kilogram
ml: Milliliter
ng: nanogram
NZW: New Zealand white

PK: Pharmacokinetic(s)
PTP(s): Previously treated patient
PUP(s): Previously untreated patient
SD: Solvent Detergent
SmPC: Core Summary of Product Characteristics
TNBP: Tri-n-butyl-phosphate
µg: microgram

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

Octanine is an antihemorrhagic whose active substance is Coagulation factor IX. It is used for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). The dosage form is composed of powder and solvent for solution for injection. After reconstitution with the supplied solvent (5 ml respectively 10 ml Water for Injections), the preparation is administered intravenously.

2. **<u>Quality aspects:</u>**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- International non-proprietary Name (INN): Human plasma coagulation factor IX (Christmas factor)
- Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Daltons. It is a vitamin-K dependent coagulation factor, which is synthesized in the liver.
- The active substance, the coagulation factor IX, is derived from human plasma. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin into thrombin, which then converts fibrinogen into fibrin and a clot is formed.

- **Manufacture, process controls and characterization:**

➢ **Manufacturer**

<u>Manufacturer 1</u>: Octapharma - Vienna (Octapharma Pharmazeutika Produktionsges.m.b.H)
Address: Oberlaaer Straße 235, A-1100 Vienna, Austria
<u>Manufacturer 2</u>: Octapharma - Lingolsheim (Octapharma S.A.S.)
Address: 72 rue du Maréchal Foch, F-67380 Lingolsheim, France

➢ **Description of Manufacturing Process and Process Controls**

- A flow chart describing the manufacturing process steps is provided.
- The manufacturing process steps of FVIII/VWF complex include Separation of Cryoprecipitate, Batch DEAE Sephadex Adsorption, Ultra- / Diafiltration, Anion exchange chromatography (DEAE-Sepharose Fast Flow), Ultrafiltration, Virus inactivation by S/D-Treatment, Heparin affinity chromatography, Virus removal by

Nanofiltration, Ultrafiltration, Formulation, Sterilizing Filtration, Aseptic Filling, Freeze Drying, Visual Inspection, and Labeling and Packaging.

- **Control of Materials**

Starting material for the manufacture of Octanine is human plasma that corresponds to the Ph. Eur Monograph "Human plasma for fractionation" in its current version.

- **Controls of Critical Steps and Intermediates**

- Control of Intermediate:
Intermediate I is frozen Octanine F protein concentrate
Intermediate II is the final Bulk (Octanine F)
- Control of Critical Steps:
Several virus inactivation steps are defined as critical steps.
- In Process control results for the consistency of Production at Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna and O Octapharma S.A.S., Lingolsheim are submitted by the manufacturer.

- **Process Validation**

The Process Validation for the OPG Vienna and the OSA France have been submitted by the manufacturers.

- **Manufacturing Process Development**

The development of the actual factor IX concentrate product is mainly based on the experience with the mono-inactivated (Solvent/Detergent-treatment only) predecessor product.
As the Solvent/Detergent treatment is only effective against lipid-enveloped viruses, a nanofiltration step has been introduced into the existing process. A virus filtration removes lipid-enveloped as well as nonlipid-enveloped viruses according to their size.

- **Characterization**

- OCTANINE F is a highly purified human coagulation factor IX (Ph.Eur.) preparation, freeze-dried. It is presented as powder and solvent for solution for injection. After reconstitution with the supplied solvent (Water for Injections, Ph.Eur.) the preparation is administered intravenously.
- Process related impurities might originate from substances leaching from the chromatographic media used.

- **Specification**

The specifications of the final bulk are provided in the MA file.

- **Analytical Procedures**

Analytical procedures and Validation of Analytical procedures are submitted by the manufacturer.

- **Batch analysis**

Batch analysis was provided with batches manufactured after the implementation of the new filters.

- **Reference Standards or Materials**

The reference standards used for testing of the parameters of the bulk are Pharmacopoeial.

- **Container closure system**

The Octanine final bulk (Intermediate 2) is stored in sterile 20 L Flex boy plastic bags.

- **Stability of drug substance**

Based on available stability data:
Approved Shelf Life: Up to 5 days
Approved Storage Conditions: 2°C to 8°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product**

- The active ingredient of Fanhdi is coagulation factor IX, which complies with Ph.Eur. Standard for Human plasma coagulation factor IX. The excipients used are heparin, lysine hydrochloride & arginine hydrochloride as stabilizers, and sodium citrate dihydrate & sodium chloride as buffering substances. The solvent used to reconstitute the product is water for injection.
- The packaging material in contact with the product consists of vials and stoppers which comply with the European Pharmacopoeia specifications.

- **Pharmaceutical Development**

➢ **Components of drug product**

- **Active Ingredient:** Coagulation factor IX, which complies with Ph.Eur. Standard for Human plasma coagulation factor IX
- **Excipients:** Heparin, lysine hydrochloride, arginine hydrochloride, sodium citrate dihydrate & sodium chloride
- **Solvent:** Water for injection

➢ **Formulation Development**

OCTANINE can be seen as a further development of OCTANYNE, an already established factor IX concentrate. In comparison to OCTANYNE an additional filtration step (Viresolve) has been introduced in the production process to increase the viral safety.

- **Physicochemical and Biological Properties**

The development of physiochemical and biological properties of the drug product is described in the Development Report provided in the MA file.

- **Manufacturing Process Development**

The development of the manufacturing process is described in the development report of the Drug Substance and Biochemical characterization submitted by the manufacturer in the MA file.

- **Container closure system and their compatibility**

The powder for solution for injection is supplied in labelled 30 ml vials of glass type I (Ph.Eur.), which are closed with halobutyl rubber stoppers (Bromobutyl stoppers) of type I (Ph.Eur.) and sealed with aluminium flip off caps. The solvent, water for injections, is supplied in labelled 5 ml glass vials Octanine F 500 IU of Type I (Ph.Eur.) quality, which are closed with rubber stoppers of Type I (Ph.Eur.) and sealed with a flip off cap. The injection set consists of the following devices for administration: 1 disposable syringe, 1 transfer set (1 filter needle and 1 double-ended needle), 1 winged infusion set and 2 alcohol swabs.

- **Microbiological Attributes**

The development of aseptic production is based on the general development of Factor IX products. In 2005 a bioburden In-process-control after sterile filtration was implemented in addition to the hitherto existing In-process-controls.

- **Compatibility**

No interactions of human coagulation factor IX concentrate products with other medicinal products are known. Octanine should, nonetheless, not be mixed with other medication during injection.

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities
- **Manufacturer(s):**

Manufacturer: Octapharma - Vienna

Name of Company: Octapharma Pharmazeutika Produktionsges.m.b.H

Address: Oberlaaer Straße 235, A-1100 Vienna

Country: Austria
Functions performed: Production from plasma to final product; visual inspection, labelling, packaging and integrity testing for product manufactured at all sites; batch release

Manufacturer: Octapharma - Lingolsheim

Name of Company: Octapharma S.A.S.
Address: 72 rue du Maréchal Foch, F-67380 Lingolsheim
Country: France
Functions performed: Production from plasma to final product, batch release

Manufacturer: Octapharma – Dessau

Name of Company: Octapharma Dessau GmbH
Address: Otto-Reuter-Str. 3, D-06847 Dessau-Roßlau
Country: Germany
Functions performed: Visual inspection, labelling, packaging and integrity testing for product manufactured at all sites

Manufacturer of Solvent:

Solupharm Pharmazeutische Erzeugnisse GmbH
Industriestr. 3
D-34212 Melsungen
Germany

- The manufacturing process steps include sterilizing filteration of the bulk solution followed by aseptic filling and freeze drying. The final steps include visual inspection followed by labeling and packaging.

- **Control of critical steps and intermediates**
  For Control of Critical Steps, In-Process Control Results and In Process Test Methods and Validations are mentioned in the MA file.

- **Process validation and / or evaluation**
  The process validation report covering the whole manufacturing process is provided in the MA file.

- **Product specification:**
  - Excipients are compendial and comply with the European Pharmacopoeia and the USP.
  - No starting materials derived from bovine origin are used.
  - The only starting material derived from animal origin is Heparin Sodium extracted from porcine intestinal mucosae.
  - No novel excipients are used.

- The product and solvent specifications comply with the European Pharmacopoeia monograph of Human coagulation factor IX "1223", and ICH guideline Q6B.
- The analytical procedures were submitted in the MA file.
- The validation of analytical procedures was submitted and done according to ICH guidelines Q2(R2).
- Octanine complies with the European Pharmacopoeia monograph "Human Coagulation Factor IX"

- **Reference Standards or Materials**
  The reference standards and materials for each test method are provided in the MA file.

- **Container closure system**
  - The immediate packaging powder for solution for injection consists of a vial (30 ml) containing the concentrate corresponding to glass type I, Ph. Eur. and the stopper made of halobutyl rubber corresponding to type I, Ph. Eur. The vial with the stopper is sealed with an aluminium flip off cap.
  - Drawings and specifications for each component are provided.

- **Stability of the drug product**
  Based on available stability data:
  Approved shelf life:
  Finished product: 2 years
  Solvent: 60 months

  Approved Storage Conditions:
  Finished product: Do not store above 25°C
  -Do not freeze.
  -Keep the vial in the outer carton in order to protect from light.

3. **Non –clinical aspect:**
   - **Pharmacodynamics:**

   No primary or secondary pharmacodynamic studies were submitted. This is considered acceptable and consistent with the EMA Guideline on the Core Summary of Product Characteristics (SmPC) for Human Plasma-Derived Factor IX Products (EMA/CHMP/BPWP/401810/2013 Rev. 1), which indicates that specific pharmacodynamic investigations are not required for plasma-derived Factor IX products, as their mechanism of action is well established.

- In vitro and In vivo safety pharmacology studies were conducted to assess the thromboembolic potential of the product; results demonstrated that the high purity of the product greatly reduced such potential.

➢ **Pharmacokinetics:**

- Octanine F 500 IU is a human plasma-derived factor IX concentrate for IV use in hemophilia B. Hence, the standard PK and toxicity studies do not apply to this product. The preclinical programme submitted is mainly concerned with evaluating the PK and toxicity of impurities due to the SD process, namely TNBP and Polysorbate 80.
- After a single IV dose of 300 µg of TNBP, only small amounts of TNBP could be detected in plasma. The half-life of TNBP was very short. TNBP demonstrated low in vivo recovery of in rats. From the dose of 300 µg/kg BW and an assumed plasma volume of 34 mL/kg BW, a maximum plasma concentration (100% in vivo recovery) of 8.8 µg/mL could be expected. In fact, the measured peak plasma concentration was 156.2 ng/mL, which equals an in vivo recovery of 1.8%.
- The maximum human single dose is expected to be ≤ 6.25 µg TNBP/kg BW, the human plasma volume is 40 mL/kg BW. Extrapolating the in vivo recovery of rats to humans would result in a peak plasma concentration of ≤ 2.8 ng/ml.

➢ **Toxicology:**

Comprehensive non-clinical safety studies have been conducted to evaluate the toxicological profile of Octanine® F and its excipients, supporting its safe use in humans.

Acute Toxicity

Acute toxicity studies demonstrated that the lowest toxic dose in animal models was 4,640 µg/kg body weight corresponding to more than 740 times the maximum human exposure level of 6.25 µg/kg, based on the maximum therapeutic dose of 125 IU/kg.

Repeated Dose Toxicity

Repeated dose toxicity studies identified the lowest systemically toxic dose to be greater than 400 µg TNBP/kg BW/day (administered intravenously), confirming a wide safety margin for repeated administration.

Mutagenicity and Carcinogenicity: Both in vitro and in vivo mutagenicity studies using tri-n-butyl phosphate (TNBP) showed no evidence of chromosomal or gene mutations, even when tested at the cytotoxic range or the maximum tolerated dose level. No carcinogenicity studies were conducted; however, this is considered acceptable given the absence of mutagenic potential and the limited posology associated with Octanine® F administration.

Reproductive and Developmental Toxicity: Embryotoxicity studies performed in rats and rabbits demonstrated no adverse effects on prenatal development at any tested dose level. Although a small number of spontaneous malformations were observed in the low-

and mid-dose groups, no malformations occurred in the high-dose group (>900 µg/kg BW, IV).
The absence of a dose–response relationship indicates that these findings were not treatment-related. Furthermore, the overall malformation rate of 1.08% was below the known spontaneous background rate (1.23%) for the animal strain used, confirming no teratogenic potential.

Local Tolerance

Administration of three different batches of Octanine® F (500 IU) via intravenous, intra-arterial, or para-venous routes in male and female New Zealand White rabbits was well tolerated, with no adverse local or systemic reactions observed compared with the control group.
-Polysorbate 80, a widely used pharmaceutical excipient, is included in the Octanine® F formulation. Given its established safety record, no additional toxicity studies of the final formulation containing Polysorbate 80 were required.

In Conclusion, the results from non-clinical evaluations confirm that Octanine® F possesses a favorable safety profile with no evidence of systemic, mutagenic, teratogenic, or local toxicity at clinically relevant exposure levels.

4. **Clinical aspect:**
A total of 3 clinical studies has been performed with Octanine-F to assess the efficacy, safety and/or pharmacokinetics of the preparation. All studies were conducted in male patients with hemophilia B.

- **Clinical Pharmacology:**

Pharmacokinetic Evaluation of Octanine-F in Patients with Severe Haemophilia B

Two clinical studies (YNE-201 and YNE-202) were conducted to evaluate the pharmacokinetic (PK) properties of Octanine-F in patients with severe haemophilia B (FIX activity < 2%).
No statistically significant differences were observed in any PK parameters between Octanine-F® and Octanyne®. The mean half-life and recovery values approximately 30 hours and 1.3 %/IU/kg, respectively were relatively long and high for both preparations compared with those reported for other FIX concentrates. These results indicate favorable pharmacological characteristics: a prolonged half-life may reduce the frequency of prophylactic infusions, while a high recovery rate is expected to enhance clinical efficacy in the management of acute bleeding episodes. Collectively, the data demonstrate that both preparations exhibit comparable pharmacokinetic profiles and are equally efficacious.

The pharmacokinetic parameter estimates were consistent across both studies and aligned with current International Society on Thrombosis and Haemostasis (ISTH) and Committee for Medicinal Products for Human Use (CHMP) recommendations. The PK properties of Octanine-F are particularly favorable, underscoring their relevance as pharmacokinetic data represent the most objective surrogate marker of efficacy. This is especially pertinent considering that factor IX exerts its physiological function within both the plasma and extravascular compartments. Further confirmation of efficacy is supported by the clinical performance of Octanine-F in the treatment and prevention of bleeding episodes, as well as during surgical interventions.

- **Clinical Efficacy:**

The primary objective of the **pivotal study (YNE-202)** was to evaluate the safety and efficacy of **Octanine F®** in patients with hemophilia B who had previously received treatment.

Results:

The findings from this study confirm the safety and efficacy of **Octanine F®** in preventing and treating bleeding episodes in patients with hemophilia B. Additionally, the limited data available from surgical procedures, including those involving continuous infusion as outlined in the study protocol, further support the product's suitability for controlling bleeding during surgery.

The comprehensive safety and efficacy data collected throughout this study indicate that **Octanine F®** is a safe and effective treatment for patients with **Factor IX (FIX) deficiency**, including its potential utility in surgical settings.

A secondary study, **YNE-203**, was conducted to assess the immunogenicity of **Octanine F®** in pediatric patients under 6 years of age with moderate to severe hemophilia B. The efficacy profile observed in this study was consistent with the expected performance of an intravenous FIX product for substitution therapy, supporting the use of **Octanine F®** in this younger population.

In conclusion, the results of these studies demonstrate that **Octanine F®** is both a safe and efficacious treatment for on-demand treatment, prophylaxis, and management of bleeding episodes during surgical procedures in patients with hemophilia B. The overall efficacy profile is favorable, positioning **Octanine F®** as a reliable option for FIX replacement therapy in both adult and pediatric populations.

- **Clinical Safety:**

To ensure the highest level of viral safety, the manufacturing process of Octanine® F incorporates two dedicated virus inactivation and removal steps: solvent/detergent treatment and nanofiltration. These steps are highly effective in eliminating potential viral contaminants,

including non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. Additionally, several other purification stages within the production process further contribute to viral clearance, reinforcing the overall safety of the product.

Clinical studies have demonstrated that Octanine® F is safe and well-tolerated for prophylactic use in both previously treated patients (PTPs) and previously untreated patients (PUPs) with haemophilia B. Evaluations of thrombogenicity parameters revealed no increased risk of thrombosis. Furthermore, the safety of Octanine® F was confirmed during and after surgical procedures—no clinical signs of thrombosis were observed in any documented cases.

In study YNE-203, conducted in children under six years of age, no safety concerns specific to the paediatric population were identified. Across all clinical studies, patients were regularly tested for the development of factor IX (FIX) inhibitors, and no inhibitors were detected in either PTPs or PUPs. These findings indicate a very low immunogenic potential for Octanine® F.

Extensive post-marketing surveillance further supports these results: no anaphylactic reactions have been reported following Octanine® F administration, and ongoing viral safety monitoring has revealed no safety signals. Even during surgical interventions, where high doses (80–90 IU/kg body weight) were administered, tolerability was consistently rated as excellent.

Overall, the robust virus inactivation process, favorable clinical safety data, and extensive real-world experience confirm Octanine® F as a safe and reliable factor IX concentrate for the treatment and prevention of bleeding episodes in patients with haemophilia B.

- **Overall Conclusion**

The results show that Octanine-F is bioequivalent to Octanyne ®, the precursor FIX product. The only difference is the addition of a nanofiltration step in the manufacturing procedure of Octanine-F. It can be concluded that Octanine F exerts an excellent safety and efficacy profile. Octanine F is considered as a valuable treatment for an efficacious and safe regular substitution therapy in patients suffering from hemophilia B.

Benefit/ Risk Discussion: In conclusion the overall benefit/risk of Octanine-F 100 IU/ml is favorable in Treatment and prophylaxis of bleeding in patients with hemophilia B (congenital FIX deficiency).

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.