EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Optivate 250IU
Optivate 500IU

Date: August 2024

Unit: Technical Assessment Unit

Assessment report

Optivate

Administrative information:

Invented name of the medicinal product:	Optivate 250IU Optivate 500IU
INN (or common name) of the active substance(s):	-For optivate 250 IU: Human Coagulation Factor VIII 250 I.U/2.5ml ; Von Willebrand Factor (VWF) 260 I.U./ml. -For optivate 500 IU: Human Coagulation Factor VIII 500 I.U/5ml ; Von Willebrand Factor (VWF) 260 I.U./ml
Marketing Authorization holder	Bio Products Laboratory Limited, Dagger Lane, Elstree, Hertfordshire, WD6 3BX - UNITED KINGDOM
Applied Indication(s):	Optivate is used to prevent and treat bleeding in patients of all age groups with haemophilia A (a congenital factor VIII deficiency in the blood).
Pharmaceutical form(s) and strength(s):	-Powder and solvent for solution of I.V. injection. - It is presented in a glass vial containing 250 IU FVIII, for reconstitution in 2.5 mL Sterilized water for injections, Ph. Eur., 500 IU FVIII, for reconstitution in 5 mL Sterilized water for injections. Ph. Eur.,
Route of administration	I.V. injection.
Approved Pack(s):	-Carton box containing: 250 IU powder in a 10 ml vial (type 1 clear glass) with a stopper (Chlorobutyl rubber), with an overseal (aluminium) and tamper evident flip-off cap (polypropylene), 2.5 ml solvent in a 5 ml vial (type 1 clear glass) stoppered with chlorobutyl rubber closure with Flurotec coating & aluminum over seals (unlacquered inside) &

	polypropylene flip-off cap, One Filter Needle device, Insert Leaflet. -Carton box containing: 500 IU powder in a 10 ml vial (type 1 clear glass) with a stopper (Chlorobutyl rubber), with an overseal (aluminium) and tamper evident flip-off cap (polypropylene), 5 ml solvent in a 5 ml vial (type 1 clear glass) stoppered with chlorobutyl rubber closure with Flurotec coating & aluminum over seals (unlacquered inside) & polypropylene flip-off cap, One Filter Needle device, Insert Leaflet.

List of abbreviations

I.V.	Intravenous
CTD	Common technical document
SOPs	Standard operating procedures
WHO	World Health Organization
MA	Marketing authorization
VWD	Von Willebrand Factor
FVIII	Factor VIII (Blood coagulation Factor 8)
IU	International unit
Ph. Eur	European pharmacopeia
BPL	Bio Products Laboratories
factor IX	Factor 9 (blood clotting factor 9)
factor X	Factor 10 (blood clotting factor 10)
TSE	Transmissible spongiform encephalopathy
WFI	Water for injection
GLP	Good Laboratory Practice
AUC	Area under the curve
MRT	mean residence time
OSE	Other Surgical Experiences with Optivate®
SAE	serious adverse event

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 7.4.2022 after providing all the required documents according to "Checklist for documents of new biological products registration file".
- Full CTD along with detailed SOPs were provided.

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

-Optivate is a factor VIII/Von Willebrand factor complex. It is in the Pharmacotherapeutic Group of Antihemorrhagics: blood coagulation factor VIII. ATC code: B02BD02.

-The Optivate factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to Von Willebrand factor in the patient‟s circulation.

-Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

-Optivate 100 IU/mL powder for solution for injection is a white or pale-yellow freeze-dried powder. It is presented in a glass vial containing 250 IU FVIII, for reconstitution in 2.5 mL Sterilised water for injections, Ph. Eur., 500 IU FVIII, for reconstitution in 5 mL Sterilised water for injections.

-Sodium chloride, sodium citrate/citric acid and calcium chloride are all common excipients for products to be administered intravenously, Polysorbate 20 has been included in the formulation to improve the solubility of the highly concentrated FVIII/VWF and trehalose to preserve the solubility of the product after freeze-drying and terminal heat treatment

-In addition to its role as a factor VIII protecting, von Willebrand mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

******the company stated that the product is not intended to treat the von Willebrand disease (VWD)***

2.Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section

1.2.2 Drug Substance (Active ingredient)

(BPL) hereby have confirmed that the active substances are neither isolated nor characterized or stored but continuously processed into the bulk and subsequently into the drug product Optivate.

For this reason, No Drug substance sections are available in the MA Dossier

2.2.3 Drug product:

-Description and Composition of the Drug Product:

- Optivate 100 IU/mL powder for solution for injection is a white or pale yellow freeze-dried powder.
- It is presented in a glass vial containing 250 IU FVIII, for reconstitution in 2.5 mL Sterilized water for injections, Ph. Eur., 500 IU FVIII, for reconstitution in 5 mL Sterilized water for injections Ph. Eur.

- Pharmaceutical Development

Components of drug product

- The active ingredients in Optivate 100 IU/mL powder for solution for injection are the plasma proteins Factor VIII (FVIII) and von Willebrand Factor (VWF).
- Excipients have been chosen that contribute to the quality of the freeze-dried plug, which in turn affects the resolution characteristics of the product.
- Both FVIII and VWF are compatible with all excipients at the concentrations used, as demonstrated by stability studies carried out on the product both in the freeze dried state and after reconstitution with Sterile Water for Injection, Ph. Eur.

- Formulation Development

- Optivate was designed as a development of BPL‟s earlier FVII product 8Y.
- The formulation of Optivate is the same as that which has been used in all clinical trials of the product. Apart from these clinical trials, no bioavailability or bioequivalence studies were considered appropriate.
- Sodium chloride, sodium citrate/citric acid and calcium chloride are all common excipients for products to be administered intravenously.
- Polysorbate 20 has been included in the formulation to improve the solubility of the highly concentrated FVIII/VWF and trehalose to preserve the solubility of the product after freeze-drying and terminal heat treatment.

- Manufacturing Process Development:

Optivate was designed as a development of 8Y, which is a combined Factor VIII (FVIII) and von Willebrand Factor (VWF) concentrate for intravenous administration and is virus inactivated by dry heat treatment. The objectives when developing Optivate were:

- ✓ To add a second independent virus inactivation/removal step to meet current regulatory guidelines.
- ✓ To preserve the VWF activity so that the concentrate can be used for treatment of von Willebrand disease (VWD) as well as haemophilia A.
- ✓ To increase the specific activity of the product.
- ✓ To increase the potency of the product without detriment to solubility.

- Microbiological Attributes

- Optivate process contains several steps, which contribute to the Microbiological safety of the finished product. These steps include two dedicated viral inactivation steps solvent/detergent treatment and dry heat treatment, as well as processes which reduce bioburden in the process solution, by centrifugation or filtration, and ultimately by sterile filtration at 0.2 µ.
- The final product is tested for sterility and pyrogenicity at release, confirming its sterile status.
- Closure integrity studies including dye bath testing and microbial challenge testing, confirm that the container closure system does not permit ingress of materials, which could jeopardise product sterility.

- Compatibility

- A study has been performed which evaluates the stability of the reconstituted product and its compatibility with the container closure system.
- The study investigated the compatibility of the reconstituted product with the container and closure by storage in the vial both upright and inverted and compatibility with the administration kit (syringe) once reconstituted.
- These studies concluded that the product is stable for a period of up to 3 hours in the vial post reconstitution and that no significant levels of trace metal ions were present as a result of leaching during this storage.
- This supports product compatibility with the vial and stopper.
- The studies which evaluated the compatibility of the product with the proposed administration kit for the administration of the product to the patient suggested that the product was compatible for up to 3 days, although further studies are required to conclusively support this time period.

- **Manufacture of the drug product:**

Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer:
Optivate is manufactured by Bio Products Laboratory Ltd (BPL) Dagger Lane, Elstree, Borehamwood WD6 3BX, United Kingdom
-The drug product manufacturing, release testing 1ry and secondary packaging sites were listed in the dossier and GMP certificates were submitted.

- Control of critical steps and intermediates

- The critical steps of the Optivate drug product manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- Process validation and / or evaluation

- Data from several manufactured batches are presented to demonstrate the manufacturing performance of the defined process at each stage. In addition, process robustness studies have been undertaken to characterize the impact of variation of process parameters beyond the defined limits.
- the detailed validation procedures for each manufacturing step is presented in the MA file and found satisfactory.

-Product specification:

- The specifications proposed for release and stability testing of the Optivate finished product comply with Ph. Eur.
- Detailed SOPs, validation protocols & reports are provided for the in-house methods
- The specifications include general characteristics, biological safety tests, viral marker tests, potency &specific activity tests
- Also tests for excipients & impurities are included in the specification sheet.
- the drug product specifications at the release and during stability studies are well justified.
- All excipients used for Optivate drug product are in compliance with Ph.Eur. requirements.
- The Sodium Heparin used for the manufacture of Optivate is of porcine origin (the only component that is from biological origin).
- BPL has received assurance from the suppliers of Sodium Heparin that it is free from TSE Agents.

-Reference Standards or Materials.

- The reference standard is qualified to serve for release and stability assays for the drug product.

-Container closure system

- **Primary Packaging:**

- Optivate is presented as a freeze-dried powder within a glass vial. This glass vial is stoppered using halobutyl freeze-drying stopper and then over sealed using a crimp-on (tamper-evident) aluminum overseal.

- **Secondary packaging:**

- Each product vial is placed in a carton (protecting the product from light), with a patient information leaflet.
- Optivate is also supplied with a separately packaged vial of sterilized water for injections Ph. Eur. of appropriate volume for reconstitution of the freeze-dried product.
- The 250 IU presentation of Optivate is supplied with either 2.5 mL or 5 mL of WFI such that 2.5 mL may be used for reconstitution, the 500 IU presentation is supplied with 5 mL WFI for reconstitution.
- The product is also supplied with a filter needle or mix2vial device. In addition, on request administration sets are provided.

-Stability of the drug product

Based on available stability data,

- the approved shelf-life is **3 years** (before opening)
- Approved storage conditions:

<u>After reconstitution:</u>

-Chemical and physical in-use stability has been demonstrated for 1 hour up to 25°C.
-From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the reconstituted medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 1 hour up to 25°C

-Do not store above 25°C.
-Do not freeze.
-Keep the vials in the outer carton in order to protect from light.

Adventitious agents:

- The Optivate finished product specification identifies several impurities (contaminants). These are qualified as being below a certain level, as identified by an acceptable upper specification limit.
- *TSE certificate* is provided to ensure that there is no significant risk of contamination

with viral adventitious agents.

3. Non –clinical aspect:

-The nonclinical development of Optivate, a highly purified human blood coagulation Factor VIII and Von Willebrand Factor (VWF) factor complex was performed following the international guidelines related to preclinical testing.

- The toxicology program of the product was conducted in compliance with Good Laboratory Practice (GLP) regulations as claimed by the applicant.

- **Pharmacology:**

- No studies on the primary and secondary pharmacodynamic effects, as well as, the safety pharmacology and pharmacokinetic studies of Optivate have not been submitted, as the FactorVIII and VWF complex is naturally endogenous human protein that act in a well-recognized and understood manner and long history of clinical use, which agree with the international guidelines

- **Toxicology:**

- Toxicity studies have been limited to one single-dose and one repeated-dose study in the mouse. This is appropriate in light of the nature of the drug substance, regarding its antigenicity in animal species. The results indicate that Optivate formulation was not toxic, even at levels 20 times higher than the clinical dose that likely to be used in human.
- Regarding the reproductive and developmental toxicity; No studies have been performed, based on the rare occurrence of hemophilia A in women. It was noted that FactorVIII and VWF complex were distributed through the plasma volume but were not detected in other body compartments.
- No Genotoxicity and Carcinogenicity studies have been performed: The lack of such studies is acceptable according to the nature of the product and is in keeping with the recommendations of international guidelines.
- It is worth mentioning, based upon a review of the published literature, the majority of the impurities of Optivate (polysorbate 20 and TnBP) are either of low toxicity as they occur naturally as human proteins and are well used in other pharmaceutical products or are present in such a low level as to be safe.

Overall conclusion: Since there is extensive clinical experience and the body of data with FactorVIII-VWF complex as replacement therapy in the treatment of Hemophilia A, as well as, the process of coagulation involving the naturally occurring human proteins FactorVIII and VWF is described in the literature and has been understood for many years, *the non-clinical programme for Optivate* ***is overall acceptable.***

4. Clinical aspect:

- All studies were conducted according to Good Clinical Practice (GCP) as claimed by the applicant.

- **Clinical Pharmacology:**
  - **Clinical Pharmacokinetics:**

- Single study was conducted to evaluate the pharmacokinetics of OPTIVATE® in patients with severe haemophilia A who had not received any factor VIII replacement therapy for at least 3 days. The main pharmacokinetic variables assessed were, as recommended: (a) incremental recovery, (b) half-life, (c) area under the curve (AUC), (d) clearance and (e) mean residence time (MRT).
- There were no statistical differences between the three pharmacokinetic profiles (last dose of previous product; first dose of Optivate, after 3 months of Optivate) for any variable and all results were as expected from prior studies.
- The pharmacokinetic analysis for half-life, clearance, MRT and incremental recovery conducted in this study, found no clinical or statistically significant difference between the subjects' current Factor VIII and OPTIVATE®.
- There are little differences between the pharmacokinetic profiles of OPTIVATE® and other Factor VIII product. No safety or tolerability issues for OPTIVATE® have been identified in this long-term study.

- **Clinical Efficacy:**

- Five clinical reports have evaluated efficacy. Four of the reports are of formal clinical trials (8vWFPK, 8vWFSE, 8vWF02 and 8VWF05); the other (OSE) is a collation of data from surgical procedures carried out with Optivate in patients already committed to one of the main two studies (8vWFPK, 8vWFSE).
- The use of Optivate in prophylaxis and as on demand therapy in adults/adolescents and young children has been found to be **effective at controlling bleeding episodes**. Patients using Optivate prophylactically had **significantly fewer bleeding episodes** compared with those using it on demand.
- Some patients using on demand therapy also administered Optivate when they did not have a bleed, as a form of preventative management, for example when they might be about to do something more strenuous than usual. A similar conclusion can be made for the young children **(8VWF05)**, although **the doses used were higher than in adults.**
- **Haemostasis was satisfactory** in all the 23 surgical procedures reported with Optivate. In three procedures, tranexamic acid was used so these cannot be adequately assessed with regard to response to Optivate.

- **Clinical safety:**

- In each of the studies, all adverse events were documented.

- Because hospitalization is categorized as a serious adverse event (SAE), when patients needed to go for surgery, the event was originally captured as SAE. **None** of the SAEs in the adults or children were regarded as **related** to OPTIVATE®. There was one death from cerebral hemorrhage 8 days after the last dose of OPTIVATE in an adult. One case of interstitial pneumonia in a young child and all the other cases were hospitalizations for surgery.
- No reports of product-related adverse reaction or virus transmission or factor VIII inhibitor development.
- The safety and tolerance profiles of OPTIVATE® do not indicate any unusual hazards.

- Finally, OPTIVATE® was well tolerated both locally and systemically.
- OPTIVATE® can be considered as a useful replacement factor VIII concentrate in the management of adult patients undergoing surgery, prevent excessive bleeding during surgery in patients with severe Haemophilia A and also useful management of young children.

➢ **Clinical Immunogenicity:**

- In the clinical studies reported here, a screen for inhibitors was assessed for **817 visits** (109 in the 8vWFPK study; 589 in the 8vWFSE study, 102 in the young children's study and 17 in the surgery study, 8vWF02).
- **All of the results are negative**. These studies have now finished long-term follow-up. Thus, there is **no evidence** to suggest that OPTIVATE® has a significant potential to induce inhibitors in PTPs. Only one PUP was included in the clinical development programme. This young boy only received two infusions of OPTIVATE®.

5. Benefit/ Risk discussion:

OPTIVATE® has been developed as, and shown by clinical trial to be, a **useful alternative** to current factor VIII concentrates for the management of adults and young children with haemophilia A.

6. General Conclusion and Recommendations if any:

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