# EDA Assessment Report for Biological Medicinal Product

**(Scientific Discussion)**

## Factor IX Grifols 250 IU /5 ml
## Factor IX Grifols 500 IU /10 ml
## Factor IX Grifols 1000 IU / 20 ml
## Factor IX Grifols 1500 IU / 30 ml

## Date: October 2024

**Unit: Technical Assessment Unit**

**Assessment report**

***Factor IX***

**Administrative information:**

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| Invented name of the medicinal product: | Factor IX Grifols 250 IU /5 ml<br>Factor IX Grifols 500 IU /10 ml<br>Factor IX Grifols 1000 IU / 20 ml<br>Factor IX Grifols 1500 IU / 30 ml |
| INN (or common name) of the active substance(s): | Human Coagulation factor 50 IU/ml |
| Marketing Authorization holder | Instituto Grifols, S.A., Can Guasch, 2. Pol. Ind . levante, 08150 Parets del Vallès, Barcelona Spain - SPAIN |
| Applied Indication(s): | Indicated for the treatment and prophylaxis (prevention) of bleeding in patients with haemophilia B (congenital factor IX deficiency). |
| Pharmaceutical form(s) and strength(s): | -Powder and solvent for solution for injection.<br>-Vial containing white or pale yellow powder and vial/syringe with water for injections (solvent).<br>-Human Coagulation factor 50 IU/ml |
| Route of administration | I.V. injection. |
| Approved Pack(s): | ❖ **For 250IU**<br>-Cartoon box containing single use vial containing nominally 250 IU , Vial : 20 ml nominal capacity , 20 mm neck finish , Type II glass vials, closed with bromo-butyl rubber stopper, aluminum crimp seal and plastic cap with insert leaflet and supplied with solvent in prefilled syringe , each vial is supplied with a prefilled syringe contains 5 ml water for injection solvent in syringe with Type I glass , 10 ml nominal capacity prefilled syringe , the |

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| | barrel is closed with bromo-butyl rubber stopper and a synthetic isoprene bromobutyl tip cap, along with the accessories for reconstitution and administration (vial adaptor, filter, 2 alcohol swabs and butterfly needle).<br><br>❖ **For 500IU**<br>-Cartoon box containing single use vial containing nominally 500 IU , Vial : 20 ml nominal capacity , 20 mm neck finish , Type II glass vials, closed with bromo-butyl rubber stopper, aluminum crimp seal and plastic cap with insert leaflet and supplied with solvent in prefilled syringe , each vial is supplied with a prefilled syringe contains 10 ml water for injection solvent in syringe with Type I glass , 10 ml nominal capacity prefilled syringe , the barrel is closed with bromo-butyl rubber stopper and a synthetic isoprene bromobutyl tip cap, along with the accessories for reconstitution and administration (vial adaptor, filter, 2 alcohol swabs and butterfly needle).<br><br>❖ **For 1000IU**<br>Cartoon box containing single use vial containing nominally 1000 IU , Vial : 50 ml nominal capacity , 20 mm neck finish , Type II glass vials, closed with bromo-butyl rubber stopper, aluminum crimp seal and plastic cap with insert leaflet and supplied with solvent in prefilled syringe , each vial is supplied with a prefilled syringe contains 20 ml water for injection solvent in syringe with Type I glass , 20 ml nominal capacity prefilled syringe , the barrel is closed with bromo-butyl rubber stopper and a synthetic isoprene bromobutyl tip cap, along with the |

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| | accessories for reconstitution and administration (vial adaptor, filter, 2 alcohol swabs and butterfly needle).<br><br>❖ **For 1500IU**<br>Carton Box containing single use vial containing nominally 1500 IU, vial : 50 ml nominal capacity ,20 mm neck finish , Type II glass vials , closed with 20 mm bromo-butyl rubber stopper, aluminum crimp seal and plastic cap with insert leaflet and supplied with solvent in vial, , each vial is supplied with a vial containing 30 ml of water for injection solvent in vial with Type 1 glass , closed with Chlorobutyl rubber stopper, the cap is shrink band of plastic that fits around the cap and neck of vials which must be torn and removed to open the container, along with the accessories for reconstitution and administration (double-ended needle, filter, 2 alcohol swabs, butterfly needle and syringe with needle). |

## List of abbreviations

| | |
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| I.V. | Intravenous |
| CTD | Common technical document |
| SOPs | Standard operating procedures |
| FIX | Factor IX |
| MA | Marketing authorization |
| IU | International unit |
| VF | Virus Filtered |
| BPL | Bio Products Laboratory |
| DEAE | diethylaminoethyl |
| GMP | Good manufacturing practice |
| PTC | Prothrombin complex |
| kDa | Kilo Dalton |
| PD | Pharmacodynamics |

| | |
|---|---|
| PK | Pharmacokinetics |
| TnBP | Tri(n-butyl) phosphate |

**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 6.12.2023 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

## Table of contents

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

-The product Factor IX Grifols is manufactured by nearly the same process and its final composition is equal to the highly purified FIX concentrate ***Replenine-VF***, manufactured by Bio Products Laboratory (Elstree, UK).

-In November 1992, BPL (Bio Products Laboratory) commenced clinical trials on a high purity FIX that was known at that time as ***9MC***. When UK product license was granted on July 1994, the product was launched under the brand-name Replenine. Subsequently, BPL added a virus filtration step to the manufacturing process; the revised product was launched in February 1998 under the name Replenine-VF.

**-Instituto Grifols, S.A. has reproduced correctly the BPL's manufacturing process and both products, Replenine-VF and Factor IX Grifols, are equivalent products.**

**-Clinical use:** Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

**-Marketing situation:** Factor IX Grifols has been authorised in Spain since February 2004 and also in Algeria, Argentina, Brazil, Chile, Kazakhstan, Kuwait, Paraguay Saudi Arabia and United Arab Emirates.

-The product is formulated and adjusted to the required F IX potency, being aseptically filled into vials which are subsequently lyophilized.

-The packaging material in contact with the product consists of vials and stoppers which comply with the European Pharmacopoeia specifications.

**2. Quality aspects:**

**1.2.1 Introduction**

**As mentioned in the aforementioned section**

**1.2.2Drug Substance (Active ingredient)**

*****Factor IX Grifols is a powder and solvent for solution, which has as active ingredient human coagulation factor IX obtained from fraction I supernatant of fresh plasma fractionation according to Cohn's method. From this purification process, the isolated active ingredient is not obtained but the final product is obtained directly.***

### 2.2.3 Drug product:

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

| | Name of the ingredients | Quantity | Units | Function | Reference |
|---|---|---|---|---|---|
| Active ingredients | Factor IX activity | 40 - 62.5[1] | IU | Active ingredient | Not applicable |
| | Protein | 0.2 -0.6 | mg | Predominantly FIX | |
| Other ingredients | Lysine | 0.03 - 0.05 | g | Stabiliser | Ph. Eur. |
| | Glycine | 0.005 - 0.04 | mmol | Stabiliser | Ph. Eur. |
| | Chloride | 0.2 - 0.4 | mmol | To adjust the tonicity of the concentrate | Ph. Eur. |
| | Sodium | 0.08 - 0.18 | mmol | Derived from use of sodium salts for buffering | Ph. Eur. |
| | Phosphate | 0.005 - 0.02 | mmol | Buffering agent | Ph. Eur. |
| | Citrate | 0.003 - 0.02 | mmol | Buffering agent | Ph. Eur. |

[1] Filled as 250 IU in 5 ml, 500 IU in 10 ml, 1000 IU in 20 ml and 1500 IU in 30 ml.

**- Pharmaceutical Development**

***"Please be informed that the licenses of Factor IX Grifols and Novix refer to the same product. Novix is a human coagulation factor IX product approved in Spain with the same composition, manufacturing process and specifications of the approved Factor IX Grifols 50 IU/ml in Spain. The only difference between the 2 products is the origin of the human plasma used as starting material. Both products include the plasma approved by the European Medicines Agency, but Factor IX Grifols 50 IU/ml also includes plasma of Spanish origin while Novix doesn't includes plasma of Spanish origin. Novix was never sold in Spain; therefore, the reference product in the country of origin is Factor IX Grifols.***
***In conclusion, please note that the reference product in the country of origin is commercialized under the name Factor IX Grifols 50 UI/ml. The name Novix mentioned in the studies of the pharmaceutical development section refers to the same product than Factor IX Grifols 50 IU/ml."***

**-Components of drug product**

- The only active ingredient of NOVIX is human coagulation factor IX obtained following a continuous purification process
- Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin-K dependent coagulation factor and it is synthesized in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X.

Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.

- The other ingredients used are the following: lysine and glycine as stabilizers, phosphate and citrate that act as buffering agents, chloride to adjust the tonicity of the concentrate, and sodium derived from use of sodium salts of the above mentioned substances.

**- Formulation Development**

- human coagulation factor IX, which is a plasma protein obtained following a continuous purification process from which the isolated active ingredient is not obtained but the final product is obtained directly.
- The composition of NOVIX, expressed as a concentration per ml of reconstituted product in water for injection, is as follows:

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| **Active ingredients** | |
| Factor IX | 40 - 62.5 IU |
| Total protein | 0.2 -0.6 mg |
| **Other ingredients** | |
| Lysine | 0.03 - 0.05 g |
| Glycine | 0.005 - 0.04 mmol |
| Chloride | 0.2 - 0.4 mmol |
| Sodium | 0.08 - 0.18 mmol |
| Phosphate | 0.005 - 0.02 mmol |
| Citrate | 0.003- 0.02 mmol |
| **Carry over constituents** | |
| Factor X | < 1 IU |
| Factor II | < 0.25 IU |
| Inter-α-Trypsin Inhibitor | < 0.4 PEU |
| Polysorbate-80 | ≤ 20µg |
| TnBP | ≤ 3.6µg |

- Dose sizes for NOVIX are 250 IU, 500 IU, 1000 IU and 1500 IU Factor IX for reconstitution in 5 ml, 10 ml, 20 ml and 30 ml of water for injection, respectively.
- The active ingredient of NOVIX, human coagulation factor IX, is present at the labelled potency, **with no overages**. Potency range is related with fiducial limits at the assay as stated in the European Pharmacopoeia in force.

**- Manufacturing Process Development**

- Instituto Grifols (IG) has developed a new, high purity factor IX concentrate, NOVIX, based on a technology transfer agreement with Bio Products Laboratory (BPL) with regard to BPL's product. Replenine-VF. IG' s objective during the development of NOVIX was to adapt the Replenine-VF

process to fit into the existing IG fractionation scheme without modifying key characteristics of process intermediates at virus reduction stages or those of the final product.

- IG has identified three main adaptations that were made to the original Replenine-VF process during development:
  *A change to the starting material used for the first stage of the Replenine-VF process: NOVIX is prepared from a prothrombin complex concentrate recovered from the fraction I supernatant using DEAE-Sephadex A50. Replenine-VF is prepared directly from cryoprecipitate supernatant.
  *Introduction of a new presentation, 1500IU, for NOVIX, additional to the 250IU, 500IU and l000IU dose sizes for Replenine-VF.
  *Adaptation of the process to IG manufacturing equipment.

**- Microbiological Attributes**

- The adjusted high purity FIX solution is sterile filtered by 0.22 µm absolute pore size membrane (MCGL, CVGL, Sartobran, SLK, or equivalent), recovering the sterile filtered bulk inside the aseptic area.
- The sterile bulk solution is aseptically filled into sterilised vials of 20 ml (250 IU and 500 IU dosage forms) and 50 ml (1000 IU and 1500 IU dosage forms), at doses of 5.0±0.5 g, 10.0±1.0 g, 20.0±2.0 g and 30.0±3.0 g, which correspond to 250 IU, 500 IU, 1000 IU and 1500 IU respective factor IX dosage forms.
- Results of the final product stability study (04/319) indicate that the vial/closure system used is able to maintain the sterility of the product at least for 36 months in all four dose presentation sizes.

**- Compatibility**

- In order to ensure that NOVIX biochemical properties remain unaltered once reconstituted, Instituto Grifols has studied the compatibility of the product with the vials and with the filters used for product filtration prior to patient administration.
- Results obtained in this study shown that Gardian filter filtration does not affect NOVIX features with regard to the analysed parameters. In addition, no significant change in FIX potency or clotting factors activation has been detected after 72 hours storage at 25ºC post-reconstitution. The appearance of the solution also remains correct during the studied time.
- The proposed shelf-life for NOVIX is initially 2 years when stored between 2 - 8 ºC.For the purpose of ambulatory use, the product may be removed from the refrigerator for one single period of maximum 3 months at room temperature.
- The results of the stability studies has been obtained from fifteen full scale manufacturing batches of high purity Factor IX NOVIX including all four 250IU, 500IU, 1000IU and 1500IU doses. These results include real stability data up to 42 months in all cases.

**-Manufacture of the drug product:**

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

**Manufacturer**:

- **Instituto Grifols, S.A., c/Can Guasch, 2, Pol. Ind. Levante, Parets del Vallés, 08150 Barcelona, Spain,** is responsible for the whole manufacturing process, i.e. from plasma starting material through to be labelled, packaged, quality control testing and batch release finished product.
  **** GMP certificates were submitted.**

**- Control of critical steps and intermediates**

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

**- Process validation and / or evaluation**

- To validate the F-IX process performed with the optional extraction of Prothrombin complex (PTC), several processes performed from February 2011 to May 2012 have been studied.
- After evaluating the overall results, it is demonstrated that the manufacturing process performed to obtain F-IX is under control and capable of manufacturing batches of plasma fractions repetitively with adequate quality.
- validation reports are attached with the MA file.

**-Product specification:**

- The specifications proposed for release and stability testing of the factor IX finished product complies with Ph. Eur.
- Detailed SOPs ,validation protocols & reports are provided for the in-house methods
- The specifications include physicochemical control, biological control & immunochrmical control.
- Also tests for excipients & impurities are included in the specification sheet.
- Justification of the drug product specifications at the release and during stability studies are provided.
- All excipients used for factorIX drug product are in compliance with Ph.Eur. requirements.

**-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:**

- **Factor IX Grifols 50 IU/ml** (**250 IU/5 ml & 500 IU/10 ml**) is filled into 20 ml nominal capacity, 20 mm neck finish, type II glass vials. Glass material meets European Pharmacopoeia. Vials are closed with a 20 mm bromo-butyl-rubber stopper for freeze-drying, which meets European Pharmacopoeia.
- **Factor IX Grifols 50 IU/ml** (**1000 IU/20 ml & 1500 IU/30 ml**) is filled into 50 ml nominal capacity, 20 mm neck finish, type II glass vials. Glass material meets European Pharmacopoeia, Vials are closed with a 20 mm ø bromo-butyl-rubber stopper for freeze-drying, which meets European Pharmacopoeia.
- The controls performed on the vials and stoppers, which are in accordance with the European Pharmacopoeia will always be adapted to the edition in force.
- certificates of analysis of the vials &stoppers are attached with the MA file.
- the packaging components of Factor IX Grifols are compatible with the product, the stability report that support compatibility is provided in the MA file.

**-Stability of the drug product**

- Based on available stability data,
  *the approved shelf-life is 36 months
  *Approved Storage Conditions: 2-8°C
  ✓ Solution should be used immediately after reconstitution or within 3 hours.
  ✓ When its ambulatory administration is suitable, the product may be kept at room temperature (do not store above 25 ºC) during a single period of maximum 3 months.
  ✓ The product must not be refrigerated again after being kept at room temperature.

**Adventitious agents:**

- **Non-viral agents: TSE elimination studies**

Instituto Grifols has carried out a study in order to estimate the capacity of Factor IX Grifols production process to eliminate prion agents in the presence of a hypothetic contamination.

- **Viral agents: Viral removal/inactivation studies.**

An evaluation has been made of the overall virus elimination capacity of the Factor IX Grifols production process for different viruses.
Various selected steps in the production process have been studied for their capacity to eliminate potential viral contamination, The results demonstrate a high level of safety against the viruses studied, as summarised in the MA file.

### 3. Non –clinical aspect:

Factor IX Grifols is a freeze-dried clotting factor IX concentrate obtained from human plasma by a continuous purification process. Factor IX is a serine protease with a molecular weight of about 56 kDa. Its synthesis in the liver is dependent on vitamin K. Factor IX is found in human plasma at a concentration of about 5 µg/ml.

The product Factor IX Grifols is manufactured by nearly the same process and its final composition is equal to the highly purified FIX concentrate Replenine-VF, manufactured by Bio Products Laboratory (Elstree, UK). Instituto Grifols, S.A. has reproduced correctly the BPL's manufacturing process, several efforts have been exerted in order to study the equivalence between both products including different manufacturing steps and final product and both products, Replenine-VF and Factor IX Grifols, are considered equivalent products as claimed by the applicant.

- **Pharmacology:**

Instituto Grifols has designed and developed an extensive In Vitro comparative study program in order to demonstrate the absolute equivalence of Factor IX Grifols manufactured by Instituto Grifols and Replenine-VF.

The results obtained in the characterization studies of the final product show that the high purity factor IX concentrate Factor IX Grifols, developed by Instituto Grifols fully complies with the specifications defined by BPL for Replenine-VF.

- **Toxicology:**

The applicant claimed that the preclinical studies conducted with Replenine-VF are applicable to Factor IX Grifols as it has been shown that the manufacturing processes are equivalent and the two products are biochemically equivalent.

The results of animal studies indicate that both acute toxicity and the thrombogenic risk of high purity factor IX concentrates Factor IX Grifols and Replenine-VF are non-existent in comparison with the control material and concentrates of factor IX complexes. In addition, low levels of carry-over constituents from the manufacturing process (Copper, Polysorbate 80 and TnBP) were observed.

**Overall conclusion:** The conducted nonclinical programme demonstrated high degree of equivalence between Replenine-VF and Factor IX Grifols regarding efficacy and safety.

*Thus, Factor IX Grifols is considered acceptable from the nonclinical point of view.*

## 4. Clinical aspect:

**Pharmacokinetics:**

- Factor-IX Grifols presents a similar pharmacokinetic profile as other FIX concentrates.
- After 6 months of treatment, Factor-IX Grifols presents a similar pharmacokinetic profile in severe hemophilic patients.
- No differences were found in terms of half-life, clearance and mean residence time.
- These data have confirmed the efficacy of one single infusion of Factor-IX Grifols to reach appropriate post-infusion levels of FIX, and to maintain these levels for an appropriate time, predicting an adequate response to Factor-IX Grifols infusion. Therefore, the human plasma derived concentrate Factor-IX Grifols shows efficacy as an alternative to the current replacement therapy in hemophilia-B.

**Pharmacodynamics:**

- According to the guideline, no formal PD studies conducted.

**Clinical Efficacy:**

- Clinical efficacy was assessed in major bleedings and in terms of long-term clinical efficacy. There were no adverse events reported, the patients did not receive concomitant medication, blood loss and bleeding length were in the expected range and there were no complications and the efficacy was estimated as excellent and good.
- Long-term clinical efficacy was assessed calculating the consumption of FIX in prophylaxis and in on-demand treatment.
- For long-term treatment, 1,446,000 IU of Factor-IX Grifols were used in 961 infusions, 30.6 % of them were for prophylaxis and 69.5 % for bleeding episodes.
- Five major bleedings were reported but just 4 were evaluated (3 were excellent and 1 was good). Overall, the clinical efficacy was considered excellent/good in most of the infusions (95.9%).
- Although there are no data on Factor-IX Grifols efficacy in surgical procedures until now, due to the similarity between Factor-IX Grifols and Replenine-VF, the efficacy of Factor-IX Grifols is supported by the large experience with Replenine-VF and the former Replenine, which support the hemostatic effectiveness of Factor-IX Grifols.

**ClinicalSafety:**

- The collected data from Factor-IX Grifols show a safe profile.

**Tolerance**: no adverse events potentially related to the study drug were reported during the pharmacokinetic studies and during the 12 months of follow up. No clinically significant changes in vital signs or in haematological and biochemical parameters were detected.

- **Thrombogenicity**: there was no evidence from laboratory studies that Factor-IX Grifols poses an increased thrombogenic risk compared to the control products; also no clinical evidence of thrombotic events was noted in the patients using Factor-IX Grifols during the follow up period. Furthermore, there have been no incidences of thrombotic complications in patients treated with Replenine-VF and Replenine.
- **Viral safety**: Factor-IX Grifols has two specific virus inactivation or removal steps included in the process which are properly validated, to increase the viral safety of the product. There were no product-related viral infections for any patient included in the study.

In conclusion, Factor-IX Grifols is a FIX concentrate well tolerated which presents a safe profile in relation to thrombogenicity and viral safety.

**Clinical Immunogenicity:**

Evaluation of immunogenicity showed no inhibitors development during the study. Lack of efficacy of the product was not observed and there were no changes in in vivo recovery and pharmacokinetic parameters at first dose and after 6 months of routine treatment. These are also evidence that no inhibitors were developed for any patient. Therefore, the cumulative incidence of inhibitors related to patient-month and to exposure-days of treatment was 0. The wide experience with the similar products, Replenine-VF and Replenine, has also demonstrated the safety profile of these FIX concentrates in terms of immunogenicity. No presence of inhibitors has been reported in previously treated patients.

- **Benefit/ Risk discussion:**

The overall conclusion is that Factor-IX Grifols, as Replenine-VF, is an active, effective and good tolerated plasma-derived FIX concentrate for replacement therapy in hemophilia-B patients.

The overall benefit risk of Factor-IX Grifols is favorable the treatment and prophylaxis of bleeding in patients with hemophilia-B (Congenital Factor-IX Deficiency).