ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Refixia 500 IU powder and solvent for solution for injection
Refixia 1 000 IU powder and solvent for solution for injection
Refixia 2 000 IU powder and solvent for solution for injection
Refixia 3 000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Refixia 500 IU powder and solvent for solution for injection

Each vial contains nominally 500 IU nonacog beta pegol*.
After reconstitution, 1 ml of Refixia contains approximately 125 IU nonacog beta pegol.

Refixia 1 000 IU powder and solvent for solution for injection

Each vial contains nominally 1 000 IU nonacog beta pegol*.
After reconstitution, 1 ml of Refixia contains approximately 250 IU nonacog beta pegol.

Refixia 2 000 IU powder and solvent for solution for injection

Each vial contains nominally 2 000 IU nonacog beta pegol*.
After reconstitution, 1 ml of Refixia contains approximately 500 IU nonacog beta pegol.

Refixia 3 000 IU powder and solvent for solution for injection

Each vial contains nominally 3 000 IU nonacog beta pegol*.
After reconstitution, 1 ml of Refixia contains approximately 750 IU nonacog beta pegol.

*recombinant human factor IX, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, covalently conjugated to a 40 kDa polyethylene-glycol (PEG).

The potency (IU) is determined using the European Pharmacopoeia one-stage clotting test. The specific activity of Refixia is approximately 144 IU/mg protein.

Refixia is a purified recombinant human factor IX (rFIX) with a 40 kDa polyethylene-glycol (PEG) selectively attached to specific N-linked glycans in the rFIX activation peptide. Upon activation of Refixia, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native activated factor IX molecule. The primary amino acid sequence of the rFIX in Refixia is identical to the Ala148 allelic form of human plasma-derived factor IX. No additives of human or animal origin are used in the cell culture, purification, conjugation, or formulation of Refixia.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white to off-white.

The solvent is clear and colourless.

pH: 6.4.

Osmolality: 272 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

Refixia can be used for all age groups.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring

Routine monitoring of factor IX activity levels for the purpose of dose adjustment is not necessary. In the clinical trial programme, dose adjustment was not performed. Mean steady state factor IX trough levels ≥ 15% were observed for all age groups, see section 5.2 for details.

Due to the interference of polyethylene glycol (PEG) in the one-stage clotting assay with various aPTT reagents, it is recommended to use a chromogenic assay (e.g. Rox Factor IX or Biophen) when monitoring is needed. If a chromogenic assay is not available, it is recommended to use a one-stage clotting assay with an aPTT reagent (e.g. Cephascreen) qualified for use with Refixia. For modified long-acting factor products, it is known that the one-stage clotting assay results are highly dependent on the aPTT reagent and reference standard used. For Refixia, some reagents will cause underestimation (30–50%), while most silica containing reagents will cause severe overestimation of the factor IX activity (more than 400%). Therefore, silica based reagents should be avoided. Use of a reference laboratory is recommended when a chromogenic assay or a qualified one-stage clotting assay is not available locally.

Posology

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

Prophylaxis

40 IU/kg body weight once weekly.
Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. The trough levels achieved with the weekly 40 IU/kg dosing regimen are summarised in section 5.2.

Patients on prophylaxis who forget a dose are advised to take their dose upon discovery and thereafter continue with the usual once weekly dosing schedule. A double dose should be avoided.

On-demand treatment

Dose and duration of the substitution therapy depend on the location and severity of the bleeding, see Table 1 for dosing guidance in bleeding episodes.

Table 1 Treatment of bleeding episodes with Refixia

Degree of haemorrhage	**Recommended dose IU/kg of Refixia**	**Dosing recommendations**
Early haemarthrosis, muscle bleeding or oral bleeding. More extensive haemarthrosis, muscle bleeding or haematoma.	40	A single dose is recommended.
Severe or life threatening haemorrhages.	80	Additional doses of 40 IU/kg can be given.

Surgery

The dose level and dosing intervals for surgery depend on the procedure and local practice. General recommendations are provided in Table 2.

Table 2 Treatment in surgery with Refixia

Type of surgical procedure	**Recommended dose IU/kg body weight**	**Dosing recommendations**
Minor surgery including tooth extraction.	40	Additional doses can be given if needed.
Major surgery.	80	Pre-operative dose.
	40	Consider two repeated doses of 40 IU/kg (in 1–3 day intervals) within the first week after surgery. Due to the long half-life of Refixia, the frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved.

Paediatric population

The dose recommendations in children are the same as for adults (for more details on paediatrics see sections 5.1 and 5.2).

Method of administration

Intravenous use.

Refixia is administered by intravenous bolus injection over several minutes after reconstitution of the powder for injection with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 ml/min.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

In case of self-administration or administration by caregiver appropriate training is needed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with Refixia. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors

After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

In case of residual FIX activity levels, there is a risk of interference when performing the Nijmegen modified Bethesda assay for inhibitor testing. Therefore a pre-heating step or a wash-out is recommended in order to ensure detection of low-titre inhibitors.

Thromboembolism

Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with Refixia should be weighed against the risk of these complications.

Cardiovascular event

In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population

The listed warnings and precautions apply both to children and adults.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free". In case of treatment with multiple vials, the total sodium content should be taken into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

Refixia has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely with recombinant factor IX products and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also section 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions has been observed.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre is contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX products like Refixia is rarely associated with such adverse reactions.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

A total of 115 previously treated patients (PTPs) and 50 previously untreated patients (PUPs) with moderate or severe haemophilia B have been exposed to Refixia for a total of 434 patient years in the completed and on-going clinical trials.

Table 3 Frequency of adverse reactions in clinical trials

System Organ Class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Factor IX inhibition	Common*
Immune system disorders	Hypersensitivity Anaphylactic reaction	Common Common*
Cardiac disorders	Palpitations	Uncommon
Gastrointestinal disorders	Nausea	Common
Skin and subcutaneous tissue disorders	Pruritus** Rash	Common Common
General disorders and administration site conditions	Fatigue Hot flush Injection site reactions***	Common Uncommon Common

* Frequency based on occurrence in PUP trial (N=50)
**Pruritus includes the terms pruritus and ear pruritus
***Injection site reactions include injection site pain, infusion site pain, injection site swelling, injection site erythema and injection site rash.

Description of selected adverse reactions

Factor IX inhibition and anaphylactic reactions have not been observed in PTPs, and frequencies are therefore based on an ongoing PUP trial with 50 patients. In this trial, Factor IX inhibition occurred in

4/50 (8%) and anaphylactic reaction occurred in 1/50 (2%) categorising these events as common. The case with anaphylactic reaction occurred in a patient that also developed Factor IX inhibition.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be similar as in adults. .

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses up to 169 IU/kg have been reported in clinical trials. No symptoms associated with overdoses have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor IX, ATC code: B02BD04.

Mechanism of action

Refixia is a purified recombinant human factor IX (rFIX) with a 40 kDa polyethylene-glycol (PEG) conjugated to the protein. The average molecular weight of Refixia is approximately 98 kDa and the molecular weight of the protein moiety alone is 56 kDa. Upon activation of Refixia, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native activated factor IX molecule.

Factor IX is a single chain glycoprotein. It is a vitamin-K dependent coagulation factor and it is synthesised in the liver. Factor IX is activated by factor XIa and by factor VII/tissue factor complex. 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. Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Clinical efficacy

The clinical trial programme included one phase 1 trial and five phase 3 multicentre, non-controlled trials. All patients had severe (factor IX level < 1%) or moderately severe (factor IX level ≤ 2%) haemophilia B.
Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical trials.

Prophylaxis

One hundred one of the previously treated patients and previously untreated patients across all age-groups were treated with a weekly prophylactic dose of 40 IU/kg where 40 (40%) of these patients had no bleeding episodes (see details below).

Pivotal trial

The pivotal trial included 74 adolescent (13–17 years) and adult (18–65 years) previously treated patients (PTPs). The trial included one open-label on-demand arm with treatment for approximately 28 weeks and two prophylaxis treatment arms with single-blind randomisation to either 10 IU/kg or 40 IU/kg once-weekly for approximately 52 weeks. When comparing the 10 IU/kg and 40 IU/kg treatments, the annualised bleeding rate for patients in the 40 IU/kg arm was found to be 49% lower than the bleeding rate (95% CI: 5%;73%) for patients in the 10 IU/kg arm ($p<0.05$).

The median (IQR) overall ABR in patients (13–65 years) treated with a prophylactic dose of 40 IU/kg once weekly was 1.04 (0.00; 4.01) whereas the traumatic ABR was 0.00 (0.00; 2.05), joint ABR was 0.97 (0.00; 2.07) and spontaneous ABR was 0.00 (0.00; 0.99).

In this pivotal trial in adolescent and adult patients, there were 70 breakthrough bleeding episodes for 16 out of 29 patients in the 40 IU/kg prophylaxis arm. The overall success rate for treatment of breakthrough bleeds was 97.1% (67 out of 69 evaluated bleeds). A total of 69 (98.6%) of the 70 bleeding episodes were treated with one injection. Bleeding episodes were treated with Refixia at 40 IU/kg for mild or moderate bleeds.

In 29 adult and adolescent patients treated, 13 patients with 20 target joints were treated for one year with a weekly prophylactic dose of 40 IU/kg. Eighteen out of these 20 joints (90%) were no longer considered target joints at the end of the trial.

On-demand treatment

In the pivotal trial there was a non-randomised arm where 15 patients were treated in an on-demand regimen with 40 IU/kg for mild or moderate bleeds and 80 IU/kg for severe bleeds. The overall success rate (defined as excellent or good) for treatment of bleeds was 95% with 98% of the bleeds treated with one or two injections.

Paediatric population

Previously treated patients (PTPs)

The efficacy and safety of Refixia for prophylaxis and treatment of bleeds were evaluated in an open-label, single arm, non-controlled phase 3 trial. In the main phase of the paediatric PTP trial, 25 patients initially enrolled at 0 to 12 years of age received routine prophylactic administration of Refixia 40 IU/kg once weekly for 52 weeks. The patients were stratified into two age groups; 12 patients were 0 to 6 years and 13 patients 7 to 12 years at the time of signing informed consent. Twenty-two patients continued on to the extension phase and out of those, 12 patients had up to 8 years of routine prophylactic treatment. Due to the long trial duration several patients crossed age-groups and 10 patients that were initially enrolled as ≤ 6 years also contributed to the age category of 7-12 years. Main efficacy results in patients ≤ 12 years separated by main and extension phase are summarised in table 4.

Table 4: Annualised Bleeding Rate (ABR) in the Paediatric PTP Trial - Main & Extension Phase – actual age groups

	Main Phase		**Extension Phase**	
Age of patient*	**≤ 6 years N=12**	**7-12 years N=14**	**≤ 6 years N=10**	**7-12 years N=20**
Mean treatment period (years)	0.86	0.92	2.39	3.09
Total ABR				
Poisson-estimated mean (95% CI)	0.97 (0.50; 1.89)	2.10 (1.34; 3.30)	1.05 (0.65; 1.69	0.58 (0.21; 1.64)

	Main Phase		Extension Phase	
Age of patient*	**≤ 6 years N=12**	**7-12 years N=14**	**≤ 6 years N=10**	**7-12 years N=20**
Median (IQR)	0.00 (0.00; 1.99)	2.00 (0.00; 3.02)	0.00 (0.00; 1.65)	0.15 (0.00; 1.29)

*Some patients contributed to both age groups.

For the main and extension phase of the trial together, the overall median/poisson-estimated ABR was 0.55/1.02 (95% CI: 0.68; 1.54) in patients ≤ 6 years and 0.52/0.84 (95% CI: 0.41; 1.75) in patients 7-12 years. The median/poisson-estimated ABR was 0/0.2 (95% CI: 0.09; 0.47) and 0/0.23 (95% CI: 0.05; 0.96) for spontaneous bleeds as well as 0.53/0.82 (95% CI: 0.55; 1.23) and 0.33/0.56 (95% CI: 0.25; 1.27) for traumatic bleeds in patients ≤ 6 years and patients 7-12 years, respectively. Treatment success (defined as excellent or good response) was concluded for 88.6% and 93.7% of bleeding episodes that occurred during prophylaxis in patients ≤ 6 years and patients 7-12 years, respectively. Five out of 25 patients (20%) did not have any bleeds throughout the trial.The mean annual consumption for prophylaxis was 2 208.6 (SD: 78.8) IU/kg and 2 324.8 (SD: 83.3) IU/kg for patients ≤ 6 years and patients 7-12 years, respectively. Two patients had target joints at baseline, which were considered resolved during the main phase. None of the patients developed new target joints in the trial.

Previously untreated patients (PUPs)

The efficacy and safety of Refixia for prophylaxis and treatment of bleeds were evaluated in an open-label, single-arm multicentre non-controlled phase 3 trial. In the main phase of the paediatric PUP trial, 47 out of 50 patients < 6 years old received 40 IU/kg once weekly and 38 patients continued on to the extension phase. Main efficacy results separated by main and extension phase are summarised in table 5.

Table 5: Annualised Bleeding Rate (ABR) in the Paediatric PUP Trial - Main and Extension Phase

	Main Phase N=47	**Extension Phase N=38**
Mean treatment period (years)	0.75	2.23
Total ABR		
Poisson-estimated mean (95% CI)	0.82 (0.34 ; 1.98)	0.58 (0.35 ; 0.96)
Median (IQR)	0.00 (0.00 ; 1.02)	0.00 (0.00 ; 0.88)

The overall median ABR was 0 for spontaneous, traumatic, and joint bleeding episodes. For the trials main and extension phase the median/poisson-estimated ABR was 0.25/0.65 (95% CI: 0.34; 1.25) for PUPs on prophylaxis. The poisson-estimated ABRs for spontaneous and traumatic bleeds were 0.14 (95% CI: 0.05; 0.43) and 0.2 (95% CI: 0.05; 0.81) throughout the trial period, respectively (the median ABRs was 0 for both).46.8% of PUPs did not experience any bleeding events. None of the paediatric patients developed target joints in the trial. The overall success rate (defined as excellent or good) for treatment of bleeds in previously untreated patients was 96% (135 out of 140). Of the 140 treated bleeds observed in 34 (68%) out of 50 patients, 124 (89%) of the bleeds were resolved with 1 injection and 13 (9%) of the bleeds were resolved with 2 injections of Refixia.

Overall haemostatic efficacy

Bleeding episodes were treated with Refixia at 40 IU/kg for mild or moderate bleeds or 80 IU/kg for severe bleeds, where one bleed was evaluated as severe. An overall assessment of haemostatic efficacy was performed by the patient or caretaker (for home treatment) or study site investigator (for treatment under health care professional supervision) using a 4-point scale of excellent, good, moderate, or poor. The overall success rate (defined as excellent or good) for treatment of bleeds in previously treated patients was 92% (626 out of 683). Of the 677 treated bleeds observed in 84 (80%) of the 105 patients, 590 (86%) of the bleeds were resolved with 1 injection and 70 (10%) of the bleeds were resolved with 2 injections of Refixia.

The success rate and dose needed for treatment of the bleeding episodes were independent of the localisation of the bleed. The success rate for treatment of bleeding episodes was also independent of whether the bleed was traumatic or spontaneous of nature.

Surgery

Three trials, of which one trial was a dedicated surgery trial, included in total 15 major and 26 minor surgery procedures (patients aged 13 to 56 years). Haemostatic effect of Refixia during surgery was confirmed with a success rate of 100% in the 15 major surgeries in the trials. All evaluated minor surgeries were performed successfully.

In a dedicated surgery trial, the efficacy analysis included 13 major surgical procedures performed in 13 previously treated adult and adolescent patients. The procedures included 9 orthopaedic, 1 gastrointestinal, and 3 surgeries in the oral cavity. The patients received 1 pre-operative injection of 80 IU/kg on the day of surgery, and post-operatively, injections of 40 IU/kg. A pre-operative dose of 80 IU/kg Refixia was effective and no patients required additional doses on the day of surgery. In the post-surgery period Day 1 to 6 and Day 7 to 13, the median number of additional 40 IU/kg doses administered was 2.0 and 1.5, respectively. The mean total consumption of Refixia during and after surgery was 241 IU/kg (range: 81–460 IU/kg).

5.2 Pharmacokinetic properties

Refixia has a prolonged half-life compared to unmodified factor IX. All pharmacokinetic studies with Refixia were conducted in previously treated patients with haemophilia B (factor IX ≤2%). The analysis of plasma samples was conducted using the one-stage clotting assay.

Steady state pharmacokinetic parameters for adolescents and adults are shown in Table 6

Table 6 Steady state pharmacokinetic parameters of Refixia (40 IU/kg) in adolescent and adult PTPs (geometric mean (CV%))

PK Parameter	**13–17 years N=3**	**≥ 18 years N=6**
Half-life ($t_{1/2}$) (hours)	103 (14)	115 (10)
Incremental Recovery (IR) (IU/ml per IU/kg)	0.018 (28)	0.019 (20)
Area under the curve $(AUC)_{0\text{-}168h}$ (IU*hours/ml)	91 (22)	93 (15)
Clearance (CL) (ml/hour/kg)	0.4 (17)	0.4 (11)
Mean residence time (MRT) (hours)	144 (15)	158 (10)
Volume of distribution (Vss) (ml/kg)	61 (31)	66 (12)
Factor IX activity 168 h post dosing (IU/ml)	0.29 (19)	0.32 (17)

Clearance = body weight adjusted clearance; Incremental recovery = incremental recovery 30 min post dosing, Volume of distribution = body weight adjusted volume of distribution at steady state. CV = coefficient of variation.

All patients assessed in the steady state pharmacokinetic session had factor IX activity levels above 0.24 IU/ml at 168 hours post dosing with a weekly dose of 40 IU/kg.

Single-dose pharmacokinetic parameters of Refixia are listed by age in Table 7.

Table 7 Single-dose pharmacokinetic parameters of Refixia (40 IU/kg) in PTPs by age (geometric mean (CV%))

PK Parameter	**0–6 years N=12**	**7–12 years N=13**	**13–17 years N=3**	**≥ 18 years N=6**
Half-life ($t_{1/2}$) (hours)	70 (16)	76 (26)	89 (24)	83 (23)
Incremental Recovery (IR) (IU/ml per IU/kg)	0.015 (7)	0.016 (16)	0.020 (15)	0.023 (11)
Area under the curve $(AUC)_{inf}$ (IU*hours/ml)	46 (14)	56 (19)	80 (35)	91 (16)
Clearance CL (ml/hour/kg)	0.8 (13)	0.6 (22)	0.5 (30)	0.4 (15)
Mean residence time (MRT) (hours)	95 (15)	105 (24)	124 (24)	116 (22)
Volume of distribution (Vss) (ml/kg)	72 (15)	68 (22)	59 (8)	47 (16)
Factor IX activity 168 h post dosing (IU/ml)	0.08 (16)	0.11 (19)	0.15 (60)	0.17 (31)

Clearance = body weight adjusted clearance; Incremental recovery = incremental recovery 30 min post dosing, Volume of distribution = body weight adjusted volume of distribution at steady state. CV = coefficient of variation.

As expected, body weight adjusted clearance in paediatric and adolescent patients was higher compared to adults. No dose adjustment was required for paediatric or adolescent patients in clinical trials.

The mean trough levels at steady state are presented in Table 8; based on all pre-dose measurements taken every 8 weeks at steady state for all patients on once weekly dosing of 40 IU/kg.

Table 8 Mean of trough levels* of Refixia (40 IU/kg) at steady state

	0–6 years N=12	**7–12 years N=13**	**13–17 years N=9**	**18–65 years N=20**
Estimated mean factor IX trough levels IU/ml (95% CI)	0.15 (0.13;0.18)	0.19 (0.16;0.22)	0.24 (0.20;0.28)	0.29 (0.26;0.33)

* Factor IX trough levels = factor IX activity measured prior to next weekly dose (5 to 10 days post dosing) at steady state.

Pharmacokinetics were investigated in 16 adult and adolescent patients of which 6 were normal weight (BMI 18.5–24.9 kg/m^2) and 10 were overweight (BMI 25–29.9 kg/m^2). There were no apparent differences in the pharmacokinetic profiles between normal weight and overweight patients.

In the paediatric PTP trial, the Factor IX mean trough levels at steady state were within the range of mild haemophilia (i.e. 0.05–0.4 IU/ml), independent of age.

In the paediatric PUP trial, the estimated mean trough level at steady state was 0.15 IU/ml in patients < 6 years old, i.e., within the range of mild haemophilia.

5.3 Preclinical safety data

A juvenile animal neurotoxicity study was conducted to evaluate the potential neurotoxicity of Refixia when intravenously administered 120-1 200 IU/kg/twice weekly in immature male rats from 3 to 13 weeks of age (corresponding to 2 to 16 years of age in humans), followed by a 13-week treatment-free period. The doses were 6-60 times higher than the weekly clinical dose of 40 IU/kg. PEG was detected by immunohistochemical staining in the choroid plexus, pituitary, circumventricular organs, and cranial motor neurons. Dosing Refixia to juvenile rats did not result in any functional or pathological effects, as measured by neurobehavioural/neurocognitive tests, including motor activity, sensory function, learning and memory as well as growth, sexual maturation, and fertility.

In a repeat dose toxicity study in monkeys, mild and transient body tremors were seen 3 hours post dosing and abated within 1 hour. These body tremors were seen at doses of Refixia (3 750 IU/kg), which were more than 90 times higher than the recommended dose for humans (40 IU/kg). No mechanism behind the tremors was identified. Tremors have not been reported in the clinical trials.

Non-clinical data reveal no concern for humans based on conventional safety pharmacology and repeated dose toxicity studies in rats and monkeys.

In repeat dose toxicity studies in rats and monkeys, 40 kDa polyethylene-glycol (PEG) was detected by immunohistochemical staining in epithelial cells of choroid plexus in the brain. This finding was not associated with tissue damage or abnormal clinical signs.

In distribution and excretion studies in mice and rats, the 40 kDa polyethylene-glycol (PEG) moiety of Refixia was shown to be widely distributed to and eliminated from organs, and excreted via plasma in urine (42–56%) and faeces (28–50%). Based on modelled data using observed terminal half-lives (15–49 days) in rat tissue distribution studies, the 40 kDa polyethylene-glycol (PEG) moiety will reach steady state levels in all human tissues within 1–4.5 years of treatment.

The exposure ratios for PEG in the choroid plexus, measured in animals at the no observed adverse effect level (NOAEL) versus predicted clinical PEG-exposure, ranged from 5-fold in the juvenile rat neurotoxicity study to 6-fold in the 26-week repeat dose toxicity study in adult rats.

Long-term studies in animals to evaluate the carcinogenic potential of Refixia, or studies to determine the effects of Refixia on genotoxicity, fertility, development, or reproduction have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium chloride
Histidine
Sucrose (E 473)
Polysorbate 80 (E 433)
Mannitol (E 421)
Sodium hydroxide (for pH adjustment) (E 524)
Hydrochloric acid (for pH adjustment) (E 507)

Solvent

Histidine
Water for injections
Sodium hydroxide (for pH adjustment) (E 524)
Hydrochloric acid (for pH adjustment) (E 507)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or reconstituted with infusion solutions other than the provided histidine solvent.

6.3 Shelf life

Unopened

2 years. During the shelf life Refixia may be stored up to 30 °C for a single period not exceeding 6 months. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton.

After reconstitution

Chemical and physical in-use stability have been demonstrated for 24 hours stored in a refrigerator (2 °C – 8 °C) and 4 hours stored at room temperature (≤ 30 °C) protected from light.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the users and would normally not be recommended for longer than 4 hours stored at room temperature (≤ 30 °C) or 24 hours in a refrigerator (2 °C – 8 °C), unless reconstitution has taken place under controlled and validated aseptic conditions. Store the reconstituted medicinal product in the vial.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage at room temperature and storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack contains:
– 1 glass vial (type I) with powder and chlorobutyl rubber stopper
– 1 sterile vial adapter for reconstitution
– 1 pre-filled syringe of 4 ml histidine solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a tip cap with a stopper (bromobutyl)
– 1 plunger rod (polypropylene).

Pack size of 1.

6.6 Special precautions for disposal and other handling

Refixia is to be administered intravenously after reconstitution of the powder with the solvent supplied in the syringe. After reconstitution the solution appears as a clear and colourless to slightly yellow liquid, free of visible particles. Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits. Store the reconstituted medicinal product in the vial.

For instructions on reconstitution of the medicinal product before administration, see the package leaflet.

The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 ml/min.

An infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters will also be needed. These devices are not included in the Refixia package.

Always use an aseptic technique.

Disposal

After injection, safely dispose of the syringe with the infusion set and the vial with the vial adapter. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1193/001
EU/1/17/1193/002
EU/1/17/1193/003
EU/1/17/1193/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 2017
Date of latest renewal: 21 Feb 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Novo Nordisk A/S
Brennum Park 25K
DK-3400 Hillerød
Denmark

Novo Nordisk A/S
Hagedornsvej 1
DK-2820 Gentofte
Denmark

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Alle
DK-2880 Bagsværd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a non-interventional post-authorisation safety study deriving from a registry of Haemophilia patients according to an agreed protocol.	Submission of study results: Q2-2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Refixia 500 IU powder and solvent for solution for injection

nonacog beta pegol
(recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 500 IU nonacog beta pegol (approx. 125 IU/ml after reconstitution),

3. LIST OF EXCIPIENTS

Powder: sodium chloride, histidine, sucrose, polysorbate 80, mannitol, sodium hydroxide, hydrochloric acid

Solvent: histidine, water for injections, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at room temperature (up to 30 °C) for a single period up to 6 months. Must not be returned to refrigerator after storage at room temperature

Date removed from refrigerator: _____

Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1193/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Refixia 500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Refixia 500 IU powder for solution for injection

nonacog beta pegol

IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Refixia 1 000 IU powder and solvent for solution for injection

nonacog beta pegol
(recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 1 000 IU nonacog beta pegol (approx. 250 IU/ml after reconstitution),

3. LIST OF EXCIPIENTS

Powder: sodium chloride, histidine, sucrose, polysorbate 80, mannitol, sodium hydroxide, hydrochloric acid

Solvent: histidine, water for injections, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at room temperature (up to 30 °C) for a single period up to 6 months. Must not be returned to refrigerator after storage at room temperature

Date removed from refrigerator: _____

Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1193/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Refixia 1 000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Refixia 1 000 IU powder for solution for injection

nonacog beta pegol

IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Refixia 2 000 IU powder and solvent for solution for injection

nonacog beta pegol
(recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 2 000 IU nonacog beta pegol (approx. 500 IU/ml after reconstitution),

3. LIST OF EXCIPIENTS

Powder: sodium chloride, histidine, sucrose, polysorbate 80, mannitol, sodium hydroxide, hydrochloric acid

Solvent: histidine, water for injections, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at room temperature (up to 30 °C) for a single period up to 6 months. Must not be returned to refrigerator after storage at room temperature

Date removed from refrigerator: _____

Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1193/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Refixia 2 000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Refixia 2 000 IU powder for solution for injection

nonacog beta pegol

IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 000 IU

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Refixia 3 000 IU powder and solvent for solution for injection

nonacog beta pegol
(recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE

Powder: 3 000 IU nonacog beta pegol (approx. 750 IU/ml after reconstitution),

3. LIST OF EXCIPIENTS

Powder: sodium chloride, histidine, sucrose, polysorbate 80, mannitol, sodium hydroxide, hydrochloric acid

Solvent: histidine, water for injections, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack contains: 1 powder vial, 4 ml solvent in a pre-filled syringe, 1 plunger rod and 1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use

Intravenous use, after reconstitution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at room temperature (up to 30°C) for a single period up to 6 months. Must not be returned to refrigerator after storage at room temperature

Date removed from refrigerator: _____

Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1193/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Refixia 3 000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Refixia 3 000 IU powder for solution for injection

nonacog beta pegol

IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 000 IU

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for Refixia

Histidine solution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 ml

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Refixia 500 IU powder and solvent for solution for injection
Refixia 1 000 IU powder and solvent for solution for injection
Refixia 2 000 IU powder and solvent for solution for injection
Refixia 3 000 IU powder and solvent for solution for injection
nonacog beta pegol

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Refixia is and what it is used for

What Refixia is
Refixia contains the active substance nonacog beta pegol. It is a long-acting version of factor IX. Factor IX is a protein naturally found in the blood that helps to stop bleeding.

What Refixia is used for
Refixia is used to treat and prevent bleeding in all age groups of patients with haemophilia B (inborn factor IX deficiency).

In patients with haemophilia B, factor IX is missing or does not work properly. Refixia replaces this faulty or missing factor IX and helps blood to form clots at the site of bleeding.

2. What you need to know before you use Refixia

Do not use Refixia
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to hamster proteins.

If you are not sure if either of the above applies to you, talk to your doctor before using this medicine.

Warnings and precautions
Traceability
It is important to keep a record of the batch number of your Refixia. So, every time you get a new package of Refixia, note down the date and the batch number (which is on the packaging after Lot) and keep this information in a safe place.

Allergic reactions and development of inhibitors
There is a rare risk that you may experience a sudden and severe allergic reaction (e.g. anaphylactic reaction) to Refixia. Stop the injection and contact your doctor or an emergency unit immediately if you have signs of an allergic reaction such as rash, hives, weals, itching of large areas of skin, redness and/or swelling of lips, tongue, face or hands, difficulty in swallowing or breathing, shortness of breath, wheezing, tightness of the chest, pale and cold skin, fast heartbeat, and/or dizziness.

Your doctor may need to treat you promptly for these reactions. Your doctor may also carry out a blood test to check if you have developed factor IX inhibitors (neutralising antibodies) against your medicine, as inhibitors may develop together with allergic reactions. If you have such inhibitors, you may have a higher risk of sudden and severe allergic reactions (e.g. anaphylactic reaction) during future treatment with factor IX.

Because of the risk of allergic reactions with factor IX, your initial treatment with Refixia should be given in a medical clinic or in the presence of health care professionals where proper medical care for allergic reactions can be provided if needed.

Talk to your doctor immediately if your bleeding does not stop as expected or if you have to significantly increase the amount of Refixia you need to stop a bleed. Your doctor will do a blood test to check if you have developed inhibitors (neutralising antibodies) against Refixia. The risk for developing inhibitors is highest in people who have have not been treated with factor IX medicines before, typically small children.

Blood clots
Tell your doctor, if any of the following apply to you as there is an increased risk of blood clots during treatment with Refixia:
- you have recently had surgery
- you suffer from other serious illness e.g. liver disease, heart disease, or cancer
- you have risk factors for heart disease e.g high blood pressure, obesity, or smoking.

Kidney disorder (nephrotic syndrome)
There is a rare risk of developing a specific kidney disorder called “nephrotic syndrome” following high doses of factor IX in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

Catheter-related problems
If you have a central venous access device (CVAD), you may develop infections or blood clots at the site of the catheter.

Other medicines and Refixia
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using Refixia.

Driving and using machines
Refixia has no influence on the ability to drive and use machines.

Refixia contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium-free”. In case of treatment with multiple vials, the total sodium content should be taken into consideration.

3. How to use Refixia

Treatment with Refixia will be started by a doctor who is experienced in the care of patients with haemophilia B. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure about how to use Refixia.

Your doctor will calculate the right dose for you. The dose will depend on your weight and what the medicine is being used for.

Prevention of bleeding
The usual dose of Refixia is 40 international units (IU) per kg of body weight. This is given as one injection every week. Your doctor may choose another dose or change how often the injections should be given, based on your need.

Treatment of bleeding
The usual dose of Refixia is 40 international units (IU) per kg of body weight. Depending on the location and the severity of bleeding you may need a higher dose (80 IU per kg) or extra injections. Discuss with your doctor the dose and number of injections you need.

Use in children and adolescents
Refixia can be used in children and adolescents of all ages. The dose in children and adolescents is also calculated according to body weight and is the same dose as for adults.

How Refixia is given
Refixia is available as powder and solvent that is made up into a solution (reconstitution) and given as an injection into a vein. See “Instructions on how to use Refixia” for more information.

If you use more Refixia than you should
If you use more Refixia than you should, contact your doctor.

If you have to significantly increase the amount of Refixia you need to stop a bleed, talk to your doctor immediately. For further information, see section 2 “Allergic reactions and development of inhibitors”.

If you forget to use Refixia
If you forget a dose, inject the missed dose as soon as you remember. Do not inject a double dose to make up for a forgotten dose. If you are in doubt contact your doctor.

If you stop using Refixia
If you stop using Refixia you may no longer be protected against bleeding or a current bleed may not stop. Do not stop using Refixia without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions are possible with this medicine.

If sudden and severe allergic reactions (e.g. anaphylactic reactions) occur, the injection must be stopped immediately. You must contact your doctor or an emergency unit immediately if you have early signs of a severe allergic reaction (anaphylactic reaction) such as:
- difficulty in swallowing or breathing
- shortness of breath or wheezing
- chest tightness
- redness and/or swelling of the lips, tongue, face or hands
- rash, hives, weals or itching
- pale and cold skin, fast heartbeat, and/or dizziness (low blood pressure).

For children not previously treated with factor IX medicines, inhibitors (see section 2) may form commonly (up to 1 in 10 patients). If this happens, the medicine may stop working properly and your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

The following side effects have been observed with Refixia:

Common side effects (may affect up to 1 in 10 people)
- allergic reactions (hypersensitivity). This may become severe and could be life-threatening (anaphylactic reactions)
- itching (pruritus)
- skin reactions at the site of injection
- feeling sick (nausea)
- feeling very tired
- rash
- Children not previously treated with factor IX medicines: neutralising antibodies (inhibitors), anaphylactic reactions.

Uncommon side effects (may affect up to 1 in 100 people)
- heart palpitations
- hot flush.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Refixia

Keep this medicine out of the sight and reach of children.

Do not use Refixia after the expiry date which is stated after “EXP” on the carton and on the vial and the pre-filled syringe labels. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Refixia may be taken out of the refrigerator for a maximum period of 6 months and stored at room temperature (up to 30 °C). Please record on the carton the date Refixia is removed from the refrigerator and placed at room temperature. This new expiry date should never exceed the one initially mentioned on the outer carton. If the medicine has not been used before the new expiry date, it should be disposed of. After storage at room temperature the medicine must not be put back in the refrigerator.

Use the injection immediately after making up the solution (reconstitution). If it cannot be used immediately, use within 24 hours if stored in a refrigerator at 2 °C – 8 °C or within 4 hours if stored out of the refrigerator at a maximum temperature of 30 °C.

The powder in the vial appears as a white to off-white powder. Do not use the powder if the colour has changed.

The reconstituted solution will be clear and colourless to slightly yellow. Do not use the reconstituted solution if you notice any particles or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Refixia contains

- The active substance is nonacog beta pegol (pegylated human coagulation factor IX (rDNA)). Each vial of Refixia contains nominally 500 IU, 1 000 IU, 2 000 IU or 3 000 IU nonacog beta pegol corresponding to approximately 125 IU/ml, 250 IU/ml, 500 IU/ml or 750 IU/ml respectively after reconstitution with histidine solvent.
- The other ingredients in the powder are sodium chloride, histidine, sucrose, polysorbate 80, mannitol, sodium hydroxide and hydrochloric acid. See section 2 “Refixia contains sodium”.
- The ingredients in the sterilised solvent are histidine, water for injections, sodium hydroxide and hydrochloric acid.

What Refixia looks like and contents of the pack

- Refixia is provided as a powder and solvent for solution for injection (500 IU, 1 000 IU, 2 000 IU or 3 000 IU powder in a vial and 4 ml solvent in a pre-filled syringe, a plunger rod with a vial adapter – pack size of 1).
- The powder is white to off-white and the solvent is clear and colourless.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions on how to use Refixia

Read these instructions carefully before using Refixia.

Refixia is supplied as a powder. Before injection a solution must be made up (reconstituted) with the solvent supplied in the syringe. The solvent is a histidine solution. The reconstituted solution must be injected into a vein (intravenous (IV) injection). The equipment in this package is designed to reconstitute and inject Refixia.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These items are not included in the Refixia package.

Do not use the equipment without proper training from your doctor or nurse.

Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medicine directly into the veins, it is important to **use a clean and germ- free (aseptic) technique.** Incorrect technique can introduce germs that can infect the blood.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it has expired. Use a new package instead. The expiry date is printed on the outer carton, on the vial, on the vial adapter, and on the pre-filled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

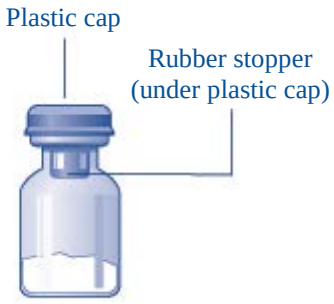
Contents

The package contains:

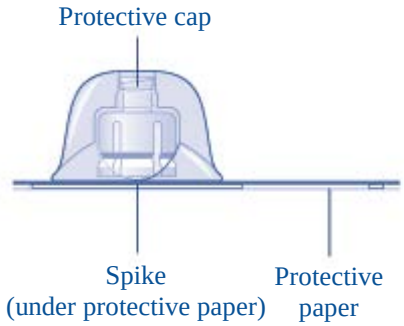
- 1 vial with Refixia powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

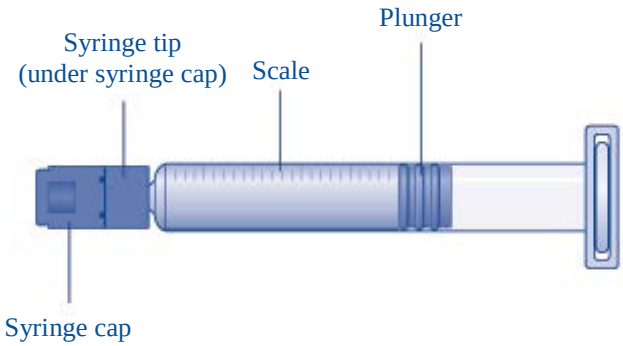
Vial with Refixia powder

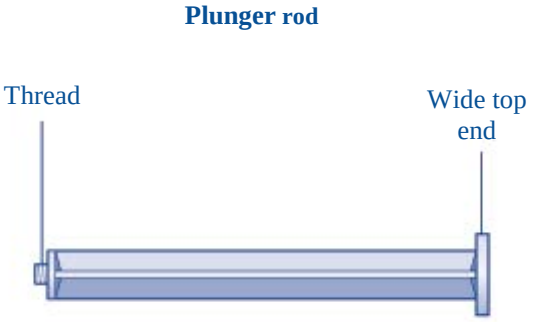


Vial adapter



Pre-filled syringe with solvent

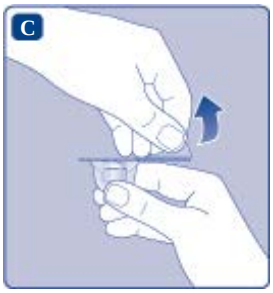
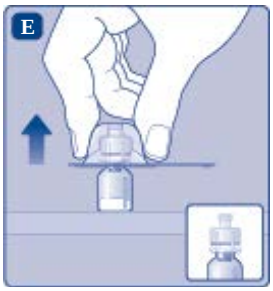
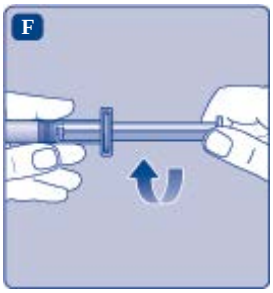


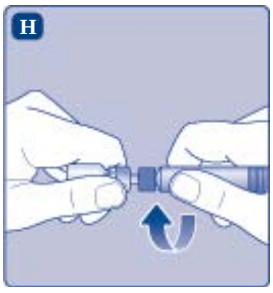
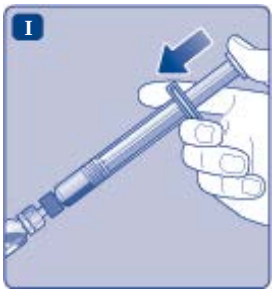


1. Prepare the vial and the syringe

- **Take out the number of Refixia packages you need.**
- **Check the expiry date.**
- **Check the name, strength and colour** of the package, to make sure it contains the correct product.
- **Wash your hands** and dry them properly using a clean towel or air dry.
- Take the vial, the vial adapter and the pre-filled syringe out of the carton. **Leave the plunger rod untouched in the carton.**
- **Bring the vial and the pre-filled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands.
- **Do not use any other way to warm** the vial and pre-filled syringe.

- **Remove the plastic cap** from the vial**. If the plastic cap is loose or missing, do not use the vial.**
- **Wipe the rubber stopper with a sterile alcohol swab** and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible.
- **Do not touch the rubber stopper with your fingers as this can transfer germs.**

2. Attach the vial adapter • **Remove the protective paper from the vial adapter.** **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter, germs from your fingers can be transferred.	
• **Place the vial on a flat and solid surface.** • **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not remove the vial adapter from the vial.**	
• Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter. **Do not lift the vial adapter from the vial** when removing the protective cap.	
3. Attach the plunger rod and the syringe • Grasp the plunger rod by the wide top end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred. • **Immediately** connect the plunger rod to the syringe by turning it clockwise into the plunger inside the pre-filled syringe until resistance is felt.	

• **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks. • **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred. **If the syringe cap is loose or missing, do not use the pre-filled syringe.**	
• **Screw the pre-filled syringe securely** onto the vial adapter until resistance is felt.	
4. Reconstitute the powder with the solvent • **Hold the pre-filled syringe slightly tilted** with the vial pointing downwards. • **Push the plunger rod** to inject all the solvent into the vial.	
• **Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** • **Check the reconstituted solution.** It must be clear and colourless to slightly yellow and no particles should be visible. **If you notice particles or discolouration, do not use it.** Use a new package instead.	

Refixia is recommended to be used immediately after it has been reconstituted. This is because if left, the medicine may no longer be sterile and could cause infections.

If you cannot use the reconstituted Refixia solution immediately, it should be used within 4 hours when stored at room temperature (up to 30 °C) and within 24 hours when stored in a refrigerator (2 °C – 8 °C). Store the reconstituted product in the vial.

Do not freeze reconstituted Refixia solution or store it in syringes.

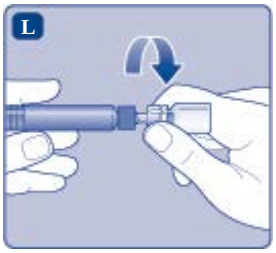
Keep reconstituted Refixia solution out of direct light.

If your dose requires more than one vial, repeat steps **A** to **J** with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.

- **Keep the plunger rod pushed completely in**.
- **Turn the syringe** with the vial upside down.
- **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe.
- **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe.
- **In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.**

  If, at any point, there is air in the syringe, inject the air back into the vial.
- While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top.
- **Push the plunger rod** slowly until all air bubbles are gone.

- **Unscrew the vial adapter** with the vial.
- **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.



5. Inject the reconstituted solution

Refixia is now ready to inject into your vein.
- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 1 to 3 minutes.
- Do not mix Refixia with any other intravenous infusions or medicines.

Injecting Refixia via needleless connectors for intravenous (IV) catheters

Caution: The pre-filled syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the pre-filled syringe. This incompatibility may prevent administration of the medicine and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:
- Use a clean and germ-free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the reconstituted solution. This should be done right after step J.
- If the CVAD line needs to be flushed before or after Refixia injection, use sodium chloride 9 mg/ml solution for injection.

Disposal

- **After injection, safely dispose** of all unused Refixia solution, the syringe with the infusion set, the vial with the vial adapter and other waste materials as instructed by your pharmacist.

  Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.

Do not reuse the equipment.