▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

Refixia® (nonacog beta pegol)

1. NAME OF THE MEDICINE

Nonacog beta pegol 500 IU powder and solvent for solution for injection
Nonacog beta pegol 1000 IU powder and solvent for solution for injection
Nonacog beta pegol 2000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 500 IU, 1000 IU or 2000 IU nonacog beta pegol.

One ml of the solution contains approximately 125 IU, 250 IU or 500 IU nonacog beta pegol, respectively after reconstitution with the accompanying histidine solvent.

The potency (IU) is determined using European Pharmacopoeia one stage clotting assay. The nominal specific activity of Refixia is 152 IU/mg protein.

Powder and solvent for solution for injection.

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. The rFIX protein in Refixia consists of a gamma-carboxylated domain (Gla domain), two epidermal growth factor-like (EGF-like) domains, an activation peptide (which is cleaved off upon activation) and a protease domain. A 40 kDa PEG-group is selectively attached to specific N-linked glycans in the rFIX activation peptide, with monoPEGylated rFIX as the predominant form of Refixia. Once activated, the resulting rFIX has structural and functional properties similar to those of plasma derived factor IX.

Refixia is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

No additives of human or animal origin are used in the cell culture, purification, conjugation and formulation of Refixia.

The rFIX protein is purified by a series of chromatographic steps, including an affinity chromatography step using a monoclonal antibody, expressed in CHO cells, to selectively isolate rFIX from the cell culture medium. The conjugation of the PEG-group is done by an enzymatic reaction during the purification of Refixia. The production process includes two dedicated and validated viral clearance steps, namely a detergent treatment step for inactivation and a 20 nm filtration step for removal of viruses.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection. For intravenous use.

The lyophilised powder is white to off-white.

The solvent is clear and colourless, free from visible particles.

Refixia is sterile, pyrogen-free and free of preservatives.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency).

4.2 Dose and Method of Administration

Dosage

Treatment should be initiated under the supervision of a health care professional experienced in the treatment of haemophilia.

Routine prophylaxis:
40 IU/kg body weight once weekly.

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

Adjustments of doses and administration intervals may be considered based on achieved FIX levels (see section 5.2 for guidance on monitoring assays) and individual bleeding tendency.

Bleeding episodes:
The dose and duration of the replacement therapy depends on the location and severity of the bleeding, see Table 1.

Table 1: Treatment of bleeding episodes with Refixia

Type of bleeding	Recommended dose IU/kg body weight	Dosing recommendations
Mild and moderate: Uncomplicated haemarthrosis, muscle bleed, oral bleed or haematoma.	40	A single dose is recommended.

Severe and life threatening: Iliopsoas, significant muscle bleed, pharyngeal, retroperitoneal, retropharyngeal, CNS.	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 including tooth extraction	40	Additional doses can be given if needed.
Major	80	Pre-operative
	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.

Maximum dose of nonacog beta pegol within 24 hours is to be 200 IU/kg and dosage should be conducted with an interval of 1 hour or longer. In case of administration for a bleeding episode and surgery, maximum single dose is to be 80 IU/kg.

When monitoring of the factor IX activity is performed, a chromogenic assay is recommended. Alternatively, a one-stage clotting assay can be used with an aPTT reagent qualified for use with Refixia see section 4.4.

Elderly people
There is limited experience with Refixia in patients of 65 years and above.

Paediatric patients
Refixia is not recommended for use in children below 12 years of age.

Previously Untreated Patients
The safety and efficacy of Refixia in previously untreated patients have not yet been established. Currently, the data are limited.

Method of Administration
Refixia is administered by intravenous bolus injection over several minutes after reconstitution of the lyophilised 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 the reconstitution process prior to administration, refer to the Consumer Medicine Information.

Refixia should not be mixed or reconstituted with infusion solutions other than the contained histidine solvent. Do not administer reconstituted Refixia in the same tubing or container with other medications.

Appropriate training is recommended before administering the product.

Missed Dose
Patients in routine 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.

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

Hypersensitivity
As with any intravenous protein product, allergic type hypersensitivity reactions including anaphylactic reactions are possible with Refixia. The product may contain traces of hamster proteins which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician who should ensure appropriate treatment.

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

Patients should be informed of the early signs of hypersensitivity reactions.

Because of the risk of severe allergic reactions seen in relation to inhibitor development with any factor IX products, the initial administrations of factor IX should be performed under medical observation where proper medical care for allergic reactions can be provided.

Inhibitors
The formation of inhibitors (neutralising antibodies) to factor IX may occur in connection with factor replacement therapy in the treatment of haemophilia B. All patients should be monitored regularly for the development of inhibitors that should be quantified in Bethesda Units (BU) using appropriate biological testing.

An association between the occurrence of a factor IX inhibitor and allergic reactions has been reported. 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 severe allergic reactions with subsequent challenge with factor IX.

Thromboembolic events
The use of factor IX containing products has been associated with thrombotic complications. Due to the potential risk of thrombotic complications, it is recommended to monitor patients

for early signs of thrombotic and consumptive coagulopathy when administering this product to patients with liver disease, post-operatively, new-born infants or 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.

Immune tolerance induction
The safety and efficacy of using Refixia for immune tolerance induction has not been established.

Nephrotic syndrome
Nephrotic syndrome has been reported following attempted immune tolerance induction therapy in haemophilia B patients with factor IX inhibitors often with a history of allergic reaction.

Monitoring factor IX activity
If monitoring is needed, it is recommended to use a chromogenic assay. When a chromogenic assay is not available, use a one-stage clotting assay with an aPTT reagent 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 used causing under- or overestimation of the factor IX activity. Silica based reagents may result in a significant overestimation of the activity of Refixia and should therefore be avoided.

Use of a reference laboratory is recommended when a chromogenic assay or a qualified one-stage clotting assay is not available locally.

Use in elderly
There is limited experience with Refixia in patients of 65 years and above.

Paediatric use
Refixia is not recommended for use in children below 12 years of age.

Effects on laboratory tests
No data available

4.5 Interaction with Other Medicines and Other Form of Interactions
No interaction studies have been performed and no interactions of Refixia with other medicinal products have been reported.

4.6 Fertility, Pregnancy and Lactation
No animal fertility, developmental or reproductive studies have been conducted with Refixia.

Effects on fertility
It is not known if Refixia can affect fertility.

Women of childbearing potential/contraception in males and females
No information available.

Use in pregnancy
Pregnancy category: B2

Based on the rare occurrence of haemophilia B (an X-linked recessive disorder) in women, experience regarding the use of factor IX during pregnancy is not available. Therefore, Refixia should only be used during pregnancy if clearly indicated.

Use in lactation
It is not known if Refixia is excreted in human milk. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during breastfeeding is not available. Therefore, Refixia should only be used during breastfeeding if clearly indicated.

4.7 Effects on Ability to Drive and Use Machines
No studies on the effect on the ability to drive and use machines have been performed. Refixia has no influence on the ability to drive and use machines.

4.8 Adverse Effects
Summary of the safety profile
Adverse drug reactions listed in this section are considered expected with Refixia.

Rarely, hypersensitivity and/or allergic reactions have been observed and may in some cases progress to severe anaphylaxis (including anaphylactic shock). Occasionally, these reactions have occurred in close temporal association with development of factor IX inhibitors (see also section 4.4). On rare occasions, patients with haemophilia B may develop inhibitors (neutralising antibodies) to factor IX. In such cases, the presence of inhibitors will manifest itself as an insufficient or lack of clinical response and it is recommended that a haemophilia centre is contacted.

Adverse events from completed clinical trials
During the clinical development program, 115 previously treated male patients were exposed to Refixia for a total of 8801 exposure days equivalent to 170 patient years. A total of 40 patients (35%) were treated for more than 2 years.

In the completed clinical trials, 98 patients (85.2%) experienced a total of 647 adverse events. The most commonly reported adverse events were nasopharyngitis, upper respiratory tract infection, contusion and cough.

Tabulated list of adverse events
Adverse events reported by more than 10% of the patients who participated in clinical trials are presented in Table 3.

Table 3: Tabulated list of adverse events reported in more than 10% of patients

SOC	Preferred term	Number of patients	% of patients	Number of events
Infections and infestations	Nasopharyngitis	19	16.5	35
	Upper respiratory tract infection	13	11.3	20
Injury, poisoning and procedural complications	Contusion	15	13.0	27

Respiratory, thoracic and mediastinal disorders	Cough	15	13.0	24
General disorders and administration site conditions	Pyrexia	13	11.3	24
Nervous system disorders	Headache	12	10.4	23

Adverse drug reactions from clinical trials

Previously treated patients

SOC	**Preferred term**	**Frequency* (%)**
Immune system disorders	Hypersensitivity Anaphylaxis Inhibitors	0.9 (1/115, uncommon) Unknown Unknown
Cardiac disorders	Palpitations	Uncommon
Gastrointestinal disorders	Nausea	Common
Skin and subcutaneous tissue disorders	Pruritus**	2.6 (3/115, common)
General disorders and administration site conditions	Fatigue Hot flush Injection site reactions***	Common Uncommon 3.5 (4/115, common)

*Number of patients with reaction by total number of unique patients exposed in all clinical studies (115)
**Pruritus includes the terms pruritus and ear pruritus ***Injection site reactions includes injection site pain, infusion site pain, injection site swelling, injection site erythema and injection site rash.

Previously untreated patients

In an ongoing trial in previously untreated patients, anaphylaxis has occurred in close temporal association with development of factor IX inhibitor following treatment with Refixia. Inhibitor development and anaphylactic reactions are more likely to occur during the early phases of replacement therapy. See section 4.4.

Paediatric population

Previously treated patients

Refixia is indicated for patients 12 years and above. No difference in the safety profile of Refixia was observed between previously treated paediatric patients and adults.

Previously untreated patients

See adverse drug reactions described above.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHAMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antihaemorrhagics: blood coagulation factor IX; ATC code B02BD04.

Mechanism of action

Factor IX is activated by factor XIa and by factor VII/tissue factor complex. Upon activation of Refixia, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native factor IX molecule. 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 administration of Refixia increases plasma levels of factor IX and can temporarily correct the coagulation defect in haemophilia B patients.

Clinical trials

Clinical efficacy, with regards to prophylaxis and treatment of bleeds, was investigated and the prophylactic effect of Refixia was confirmed in children and adults. The median annualised bleeding rate (ABR) was 1.00 and the median annualised spontaneous bleeding rate (AsBR) was 0.00.

Bleedings were evaluated according to a 4-point scale of excellent, good, moderate, or poor and the overall success rate (defined as excellent or good) for treatment of bleeds was 93%.

The completed clinical trial programme included one phase 1 trial and four phase 3 multicentre, non-controlled trials. The objectives of the phase 3 trials were to evaluate the safety and efficacy of Refixia in routine prophylaxis, control and prevention of bleeding episodes, and perioperative management in previously treated male patients with haemophilia

Table 4: Annualised bleeding rate in clinical trials NN7999-3774 and NN7999-3747 with 40 IU/kg (Median (IQR))

	Prophylaxis <13 years N=25	**Prophylaxis 13 to 65 years N=29**	**Prophylaxis all patients 0 to 65 years N=54**
Median annualised spontaneous bleeding rate	0.00 (0.00; 0.00)	0.00 (0.00; 0.99)	0.00 (0.00; 0.80)
Median annualised traumatic bleeding rate	0.68 (0.00; 1.93)	0.00 (0.00; 2.05)	0.00 (0.00; 1.96)
Median annualised joint bleeding rate	0.00 (0.00; 0.80)	0.97 (0.00; 2.07)	0.00 (0.00; 1.97)
Median annualised overall bleeding rate	1.00 (0.00; 2.06)	1.04 (0.00; 4.01)	1.03 (0.00; 2.89)

An overall assessment of efficacy was performed by the patient (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 when pooling all trials (NN7999-3774, NN7999-3747, NN7999-3773, NN7999-3775 [extension trial]) was 93% (551 out of 591) (See Table 5). Of the 597 treated bleeds observed in 79 (75%) of the 105 patients, 521 (87%) of the bleeds were resolved with 1 injection and additional 60 (10%) of the bleeds were resolved with 2 injections of Refixia (See Table 6).

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.

Table 5: Efficacy in control of bleeding episodes

Success rate	**N=591***
Excellent or good	551 (93%)
Moderate or poor	40 (7%)

*six bleeding episodes with missing haemostatic response.

Table 6: Number of injections to treat bleeding episodes

New bleeding episodes	**N=597**
1 injection	521 (87%)
2 injections	60 (10%)
3 or more injections	16 (3%)

Target joints

Of 29 adult and adolescent patients (trial NN7999-3747), 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.

Surgery

Two trials investigated the haemostatic effect in surgery, and included in total 16 major surgeries. Haemostatic effect of Refixia during surgery was confirmed with a success rate of

100% in all major surgeries. In addition, the haemostatic effect was assessed in 18 minor surgeries and rated as successful, and 2 minor surgeries were not evaluated regarding haemostatic effect.

In the dedicated surgery trial (NN7999-3773), the efficacy analysis of Refixia in perioperative management included 13 major surgical procedures performed in 13 previous 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 Refixia 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 to 460 IU/kg).

Pivotal clinical trial

The pivotal trial (NN7999-3747) included 74 adolescent (13 to 17 years) and adult (18 to 65 years) previously treated patients. 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. Only the 40 IU/kg prophylactic dose met the pre-specified reduction in annualised bleeding rate compared to a clinically relevant historical annualised bleeding rate. The difference between the annualised bleeding rates was not statistically significant (p=0.097).

Table 7: Annualised bleeding rate – full analysis set

	Prophylaxis		
	10 U/kg	**40 U/kg**	**Both**
Number of patients	30	29	59
Number of patients with bleeds, N (%)	25 (83.3)	16 (55.2)	41 (69.5)
Number of bleeds	132	70	202
Bleeds per patient (min ; max)	0.0 ; 17.0	0.0 ; 17.0	0.0 ; 17.0
Mean treatment period (years)	0.97	0.96	0.96
Individual ABRs			
N	30	29	59
Mean (SD)	4.81 (5.41)	3.53 (7.41)	4.18 (6.44)
Median	2.93	1.04	2.04
Interquartile range	0.99 ; 6.02	0.00 ; 4.00	0.00 ; 5.00
Min ; Max	0.00 ; 18.13	0.00 ; 37.78	0.00 ; 37.78
Poisson estimate of ABR	4.56	2.51	3.55
95% CI	3.01 ; 6.90	1.42 ; 4.43	2.53 ; 4.98
P-value*	0.402	0.013	0.040
Estimated ABR reduction**			
40 U/kg vs. 10 U/kg			0.45
95% CI			-0.11 ; 0.73
P-value***			0.097

Based on a Poisson regression model with dose as a factor allowing for over-dispersion and using treatment duration as an offset.

*P-values are from the 1-sided test of the null hypothesis that the ABR is at least 4.8 evaluated at the 2.5% level.

**Reduction = 1 - ABR relative risk. Positive values indicate a decrease in bleeding rate and negative values indicate an increase.
***2-sided test of the null hypothesis that there is no difference between the two doses evaluated at the 5% level.

The treatment period for the paediatric trial was 52 weeks. The trial included 25 paediatric previously treated patients (ages 0 to 12 years) who received a prophylactic dose 40 IU/kg once weekly.

Across trials, bleeding episodes were treated with Refixia at 40 IU/kg for mild or moderate bleeds or 80 IU/kg for severe bleeds.

Prophylactic treatment
The results of the 40 IU/kg prophylactic dose (trials NN7999-3774 and NN7999-3747) are shown in Table 8 and Table 9.

Table 8: Annualised bleeding rates in patients (0-65 years) treated with a prophylactic dose of 40 IU/kg once weekly (Median (IQR))

	Previously treated patients (factor IX<2%)			
	0-6 years N=12	7-12 years N=13	13 to 17 years N=9	18 to 65 years N=20
Annualised spontaneous bleeding rate	0.00 (0.00;0.00)	0.00 (0.00;0.68)	0.00 (0.00;0.00)	0.00 (0.00;1.51)
Annualised traumatic bleeding rate	0.00 (0.00;1.48)	0.68 (0.00;1.93)	1.93 (0.00;3.87)	0.00 (0.00;1.01)
Annualised joint bleeding rate	0.00 (0.00;0.00)	0.68 (0.00;1.63)	0.97 (0.00;2.17)	0.51 (0.00;2.04)
Annualised overall bleeding rate	0.00 (0.00;1.78)	2.00 (0.68;2.89)	1.93 (0.00;4.01)	1.03 (0.00;4.01)

Table 9: Haemostatic results in patients (0-65 years) treated with a prophylactic dose of 40 IU/kg once weekly

	Previously treated patients (factor IX<2%)			
	0-6 years N=12	7-12 years N=13	13 to 17 years N=9	18 to 65 years N=20
Haemostatic response success rate	91%	94%	100%	96%
Bleedings treated with 1 or 2 injections	91%	100%	100%	98%

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 94% (missing's are included as failure) with 98% of the bleeds treated with one or two injections.

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

-stage clotting assay. Steady-state pharmacokinetic parameters for adolescents and adults (trial NN7999-3747) are shown in Table 10.

Table 10: Steady-state pharmacokinetic parameters of Refixia (40 IU/kg) in adolescents and adults (geometric mean (CV))

PK parameter	**13-17 years N=3**	**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 PK 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 in children, adolescents and adults are listed by age in Table 11 (trials NN7999-3774 and NN7999-3747).

Table 11: Single-dose pharmacokinetic parameters of Refixia (40 IU/kg) in paediatrics, adolescents and adults by age (geometric mean (CV))

PK parameter	**0-6 years N=12**	**7-12 years N=13**	**13 to 17 years N=3**	**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*hour/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)	72.3 (15)	68.3 (22)	58.6 (8)	47.0 (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. However, no dose adjustment was required in paediatric and adolescent patients.

The estimated mean steady-state trough levels during trials (NN7999-3774 and NN7999-3747) with weekly dosing of 40 IU/kg can be found in Table 12.

Table 12: Factor IX trough levels* of Refixia (40 IU/kg) by age at steady–state

	0-6 years N=12	**7-12 years N=13**	**13 to 17 years N=9**	**18 to 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 all visits.

Steady-state factor IX activity profiles were simulated using a one-compartment distribution model with first-order elimination with PK parameters of clearance (CL) and volume of distribution (Vss) at steady state. Haemophilia B patients (older than 13 years) treated once weekly with 40 IU/kg Refixia are predicted to have a factor IX activity higher than 0.40 IU/ml for 130 hours out of 168 hours equal to approximately 80% of the week.

Pharmacokinetics were investigated in 16 adult and adolescent patients of which 6 were normal weight (BMI 18.5-24.9 kg/m2) and 10 were overweight (BMI 25-29.9 kg/m2). There were no apparent differences in the pharmacokinetic profiles between normal weight and overweight patients. The pharmacokinetic parameters were not affected by BMI.

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.

5.3 Preclinical Safety Data

Refixia was intravenously administered in repeat-dose toxicity studies in immune-deficient rats (40-1200 IU/kg/week for 26 weeks) and immune-competent monkeys (350-3750 IU/kg/week for four weeks). Polyethylene-glycol (PEG) was detected by immune-histochemical staining in epithelial cells of the choroid plexus in the majority of animals. PEG was not detected in brain tissue. This finding was not associated with morphological changes or abnormal clinical signs in these studies.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Powder: Sodium chloride, Histidine, Sucrose, Polysorbate 80, Mannitol, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment).

Solvent: Histidine, Water for injection, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment).

6.2 Incompatibilities
This medicinal product should not be mixed with other medicinal products.

6.3 Shelf Life
Unopened
24 months at 2ºC - 8ºC during which product may be stored at up to 30ºC for a single 6 month period. 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
The reconstituted product should be used immediately.

Chemical and physically in-use stability have been demonstrated for 24 hours stored in refrigerator (2ºC -8ºC) and 4 hours stored at room ºC). To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold °C) for not more than 4 hours or at 2°-8°C for not more than 24 hours.

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.

6.4 Special Precautions for Storage
Store refrigerated (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

For storage at room temperature and storage conditions after reconstitution of Refixia see section 6.3.

6.5 Nature and Contents of Container
Each pack of Refixia 500 IU, 1000 IU or 2000 IU powder and solvent for solution for injection contains:

1 glass vial (type I) with powder and chlorobutyl rubber stopper
1 sterile vial adapter for reconstitution

1 prefilled 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).

The rubber stopper or plunger has not been made with natural rubber latex.

6.6 Special Precautions for Disposal

The product is for single use in one patient on one occasion only. Contains no antimicrobial preservative. Discard any residue.

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.

6.7 Physicochemical Properties

Chemical structure
CAS name: Blood coagulation factor IX (synthetic human isoform rFIX) 40-kilodalton pegylated.

CAS number
CAS Registry Number is 1175512-71-6.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
A.B.N. 40 002 879 996
Level 3
21 Solent Circuit
Baulkham Hills NSW 2153

9. DATE OF FIRST APPROVAL

4 September 2019

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information