1. NAME OF THE MEDICINAL PRODUCT

Refixia 1000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Refixia 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU nonacog beta pegol*.
After reconstitution, 1 ml of Refixia contains approximately 250 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 pretreated patients with haemophilia B (congenital factor IX deficiency).

4.2 Posology and method of administration

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

Previously untreated patients
The safety and efficacy of Refixia in previously untreated patients have not yet been established.

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 above 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	80	Additional doses of 40 IU/kg can be given.

haemorrhages.		

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.

Children and adolescents
The same dose is recommended for children as for adults: 40 IU/kg body weight.

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 of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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 (rDNA) 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.

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

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 sodim 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 male patients with moderate or severe haemophilia B have been exposed to Refixia for a total of 170 patient years in the completed clinical trials.

Table 3 Frequency of adverse reactions in clinical trials

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity Anaphylaxis Inhibitors	Uncommon Unknown Unknown
Cardiac disorders	Palpitations	Uncommon
Gastrointestinal disorders	Nausea	Common

Skin and subcutaneous tissue disorders	Pruritus*	Common
General disorders and administration site conditions	Fatigue Hot flush Injection site reactions**	Common Uncommon Common

*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.

Previously untreated patients:
In an ongoing trial in previously untreated patients, anaphylaxis has occurred in close temporal association with development of factor IX inhibitors following treatment with Refixia®. The probability of developing inhibitors or an anaphylactic reaction are elevated in the early phases of substitution treatment (see section "Special warnings and precautions").

Description of selected adverse reactions
In an ongoing trial in previously untreated patients, anaphylaxis has occurred in close temporal association with development of factor IX inhibitors following treatment with Refixia. There are insufficient data to provide information on inhibitor incidence in previously untreated patients.

Children and adolescents
Previously treated patients: No differences in the safety profile of Refixia® were detected between previously treated children and adults.
Previously untreated patients: See adverse reactions under "Tabular presentation of adverse reactions" - "Adverse reactions in previously untreated patients".

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il.

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 completed clinical trial programme included one phase 1 trial and four phase 3 multicentre, non-controlled trials.

Prophylaxis
Fifty-four of the patients across all age-groups were treated with a weekly prophylactic dose of 40 IU/kg where 23 (43%) of these patients had no bleeding episodes.

Pivotal trial
The pivotal trial included 74 adolescent (13–17 years) and adult (18–65 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. 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 annual bleeding rate (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).
Of note, ABR is not comparable between different factor concentrates and between different clinical trials.

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.

Children and adolescents

A trial including 25 paediatric previously treated patients (ages 0–12 years) who received a prophylactic dose 40 IU/kg once weekly was performed.
In children aged 0–12 years, the median (IQR) annualised bleeding rate was 1.0 (0.00; 2.06) and the spontaneous bleeding rate was 0.00 (0.00; 0.00).

For treatment of bleeds in paediatrics, the overall success rate (defined as excellent or good) was 93% (39 out of 42 bleeds), where 36 (86 %) of the bleeds were resolved with 1 injection, and 5 (12%) of the bleeds were resolved with 2 injections of Refixia.

The European Medicines Agency has deferred the completion of the study with Refixia in previously untreated patients (see section 4.2 for information on paediatric use).

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 was 93% (551 out of 591). Of the 597 treated bleeds observed in 79 (75%) of the 105 patients, 521 (87%) of the bleeds were resolved with 1 injection and 60 (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 4

Table 4 Steady state pharmacokinetic parameters of Refixia (40 IU/kg) in adolescents and adults (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 5. The use of Refixia in children below 12 years is not indicated.

Table 5 Single-dose pharmacokinetic parameters of Refixia (40 IU/kg) 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 6; based on all pre-dose measurements taken every 8 weeks at steady state for all patients on once weekly dosing of 40 IU/kg. The use of Refixia in children below 12 years is not indicated.

Table 6 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.

5.3 Preclinical safety data

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 1–2 years of treatment.

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

Solvent
Histidine
Water for injections

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

The expiry date of the product is indicated on the packaging material .
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. MANUFACTURER:

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

8. REGISTRATION HOLDER

Novo Nordisk Ltd.
1 Atir Yeda St.
Kfar-Saba, 4464301

9. REGISTRATION NUMBER:

Refixia 1000 IU: 172-35-37303-00

Approved by MOH in May-2023

Refixia 1000 IL SPC FEB 2023