PRODUCT INFORMATION

NOVOTHIRTEEN®

NAME OF THE MEDICINE

Recombinant human factor XIII (rFXIII) 2500 IU (15 mg) powder and solvent for solution for injection

catridecacog (rys)

CAS number: 606138-08-3

DESCRIPTION

NovoThirteen contains catridecacog, a recombinant coagulation factor XIII A-subunit with a molecular mass of approximately 83.2 kDa. Catridecacog is produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology, without the use of animal derived materials.

One vial of NovoThirteen contains 2500 IU catridecacog per 3 mL, after reconstitution, corresponding to a concentration of 833 IU/mL. The specific activity of rFXIII is approximately 165 IU/mg protein.

NovoThirteen powder contains the following excipients: sodium chloride, sucrose, polysorbate 20, L-histidine, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment).

Solvent contains: Water for injection.

The potency of this medicinal product is expressed in international units (IU). These units are not interchangeable with the units used to express the potency for other FXIII-containing products.

NovoThirteen is supplied as a white lyophilised powder to be reconstituted with solvent for injection. The solvent is clear and colourless. The reconstituted solution has a pH of approximately 8.0.

PHARMACOLOGY

Pharmacodynamics

FXIII is the terminal enzyme in the blood coagulation cascade. When activated by thrombin at the site of vessel wall injury, FXIII plays an important role in the maintenance of haemostasis through cross-linking of fibrin and other proteins in the fibrin clot.

At present there are no markers that can quantitatively assess the *in vivo* pharmacodynamics of FXIII. The results of standard coagulation tests are normal, as it is the quality of the clot that is affected. A clot solubility assay is widely used as an indicator of FXIII deficiency, but

the assay is qualitative, and when performed correctly the test is positive only when the FXIII activity in the sample is close to zero.

In plasma, FXIII circulates as a heterotetramer [A_2B_2] composed of 2 FXIII A-subunits and 2 FXIII B-subunits held together by strong non-covalent interactions. The FXIII B-subunit acts as carrier molecule for the FXIII A-subunit in circulation, and is present in excess in plasma. When FXIII A-subunit is bound to FXIII B-subunit [A_2B_2], the half-life of the FXIII A-subunit [A_2] is prolonged. FXIII is a pro-enzyme (pro-transglutaminase), which is activated by thrombin in the presence of Ca^{2+}. The enzymatic activity resides with the FXIII-A subunit. Upon activation, the FXIII A-subunit dissociates from the FXIII B-subunit and thereby exposes the active site of the FXIII A-subunit. The active transglutaminase cross-links fibrin and other proteins resulting in increased mechanical strength and resistance to fibrinolysis of the fibrin clot and contributes to enhanced platelet and clot adhesion to the injured tissue.

rFXIII is a pro-transglutaminase (rFXIII [rA_2] homodimer) which is identical to the human FXIII A-subunit [A_2]. rFXIII A-subunit binds to free human FXIII B-subunit resulting in a heterotetramer [rA_2B_2] with a similar half-life to endogenous [A_2B_2]. rFXIII is activated by thrombin in the presence of Ca^{2+}. Activated rFXIII increases the mechanical strength of fibrin clots, thereby retarding fibrinolysis in a dose-dependent manner. rFXIII enhances platelet adhesion to the site of injury. Thus, rFXIII has been shown to have the same pharmacodynamic properties in plasma as endogenous FXIII.

Pharmacokinetics

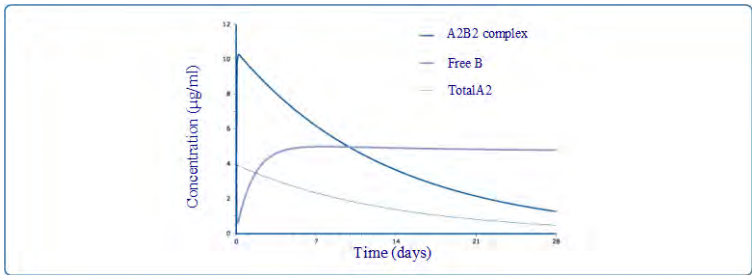


Figure 1 Simulated example of Total A_2, A_2B_2 complex and Free B in plasma as determined by ELISA following single intravenous administration of 35 IU/kg to FXIII-deficient patients

Assessment of the pharmacokinetics properties of rFXIII in healthy subjects and in patients with congenital FXIII deficiency was based on assays developed to measure plasma concentrations of FXIII subunits (individual dimers or complexes) and FXIII activity. ELISA methods were developed to measure free B_2, A_2 in complex with B_2 [rA_2B_2, A_2B_2] and total A_2 [rA_2, A_2, rA_2B_2, A_2B_2]. The total FXIII activity from both endogenous and exogenous protein was measured by the Berichrom® assay.

rFXIII has shown to have the same pharmacokinetic properties as endogenous FXIII A-subunit [A_2] following binding to endogenous FXIII B-subunit [B_2].

When rFXIII [rA_2] is administered to FXIII A-subunit deficient patients or to healthy subjects, rA_2 forms a heterotetramer complex [rA_2B_2] with free B-subunit resulting in a

rapid decrease of the plasma concentration of free B-subunit after rFXIII administration. In parallel to this, a rapid increase is observed for the concentration of the heterotetramer [rA_2B_2, A_2B_2]. After the initial decline, the pool of free B-subunit increases gradually following administration of rFXIII. Following administration of 20, 50 or 75 U/kg (corresponding to 24, 60 and 89 IU/kg, respectively) of rFXIII to patients, the plasma concentrations of free B-subunit were essentially restored to pre-dose levels within 72 hours.

The resulting half-life observed in clinical single-dose trials in healthy subjects (UKHV-1) was in the range of 218 to 321 hours (9-13 days) based on FXIII activity (Berichrom®), total A_2 (ELISA) and A_2B_2 (ELISA). Plasma clearance was observed to be in the range of 0.15 to 0.25 ml/h/kg. Pharmacokinetic parameters of rFXIII obtained in patients with congenital FXIII deficiency (CD-1) were comparable to those in healthy subjects (UKHV-1).

In a single dose trial, of 35 IU/kg of rFXIII, in healthy male subjects the following geometrical mean values of pharmacokinetics parameters were estimated based on baseline-adjusted Berichrom® data. Clearance was 0.13 mL/h/kg, the half-life was 11.1 days and volume of distribution at steady state was 47.1 mL/kg. The initial baseline-adjusted geometrical mean activity at 30 minutes post-dosing was 0.85 IU/mL (CV=24.2%) which decreased to 0.11 IU/mL (CV=85.5%) 28 days post-dose. The mean $AUC_{0\text{-}28days}$ was 220.3. IU*h/mL (CV=23.8%) and the mean AUC_{∞} 277.6 IU*h/mL (CV=47.2%).

The PK results have been summarized in Table 1 below for the clinical studies F13CD-1725, F13CD-3720 and F13CD-3760. In summary, systemic exposure to rFXIII activity (AUC0-30 days) in children aged 1 to < 6 years with congenital FXIII deficiency was similar to that in adults with the condition.

Table 1: Pharmacokinetic parameters for different age groups (F13CD-3760, F13CD-1725 and F13CD-3720 results)

Geometric mean (CV,%)	*F13CD-3760	†F13CD-1725			**F13CD-3720
	1–5 years	6–11 years	12–17 years	18+ years	7-58 years
Patients, *n*	6	9	6	26	33
$AUC_{0\text{-}28}$, IU·h/mL*	248.6 (13)	251.7 (26)	217.1 (19)	245.2 (22)	
C_{max}, IU/mL	0.67 (21)	0.75 (43)	0.67 (15)	0.76 (21)	
Trough, IU/mL	0.20 (22)	0.20 (25)	0.17 (28)	0.18 (22)	0.21 (19)
$T_{½}$, days	15.0 (34)	12.4 (21)	11.9 (32)	11.6 (18)	
CL	0.15 (12)	-	-	-	
Vss	85.7 (34)	-	-	-	

The table presents geometrical means (CV %).

*For F13CD-3760, $AUC_{0\text{-}30}$ is presented.

†For F13CD-1725, PK calculations were based on a more sparsely sampled curve (three time points vs. six time points for F13CD-3760 and F13CD-3720).

AUC, area under the concentration vs. time curve; Cmax, maximal measured FXIII activity; CV, coefficient of variance; T1/2, terminal half-life.

**Only 6 months data until Feb. 11. 2011

CLINICAL TRIALS

A pivotal prospective, open-label, single-arm phase 3 trial (F13CD-1725) including 41 patients with FXIII A-subunit deficiency was conducted to investigate the haemostatic efficacy of NovoThirteen in patients with congenital FXIII deficiency, as reflected by the rate of bleeding episodes requiring treatment with a FXIII-containing product. The dosing scheme used was 35 IU/kg/month (every 28 days +/- 2 days) administered as an intravenous bolus injection.

Five bleeding episodes requiring treatment with a FXIII-containing product have been observed in four patients during treatment with NovoThirteen in the trial.

The mean rate of treatment requiring bleeds was determined to be 0.138 per subject year, when calculated for all 41 patients. In the primary endpoint analysis, the age-adjusted rate (number per subject year) of treatment-requiring bleeds during the rFXIII treatment period was 0.048/year (95% CI: 0.009 - 0.250; model-based estimate corresponding to the mean age of 26.4 years).

Comparing with retrospectively collected data from patients with congenital FXIII deficiency, the bleeding frequency in the F13CD-1725 trial is numerically lower than the bleeding frequency for patients on regular replacement therapy (n=60) (on average approximately 0.3 treatment-requiring bleeds/year) and significantly lower than the rate of 2.91 treatment-requiring bleeds/year in patients receiving on-demand treatment (n=16).

Paediatric population
Six children (1-4 years of age), 9 children (6-12 years of age) and 6 adolescents (13-17 years of age) have been treated with NovoThirteen for a total of 277 exposures. Analyses of data from paediatric patients included in clinical trials have not identified differences in treatment response according to age.

INDICATIONS

NovoThirteen is indicated for routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency.

CONTRAINDICATIONS

NovoThirteen is contraindicated in patients with a known hypersensitivity to, rFXIII or any of the excipients of NovoThirteen.

PRECAUTIONS

General

NovoThirteen should not be used for prophylactic treatment of bleeding in patients with congenital FXIII B-subunit deficiency. FXIII B-subunit deficiency is associated with a much reduced half-life of the administered pharmacologically active A-subunit. The subunit deficiency of patients should be known prior to treatment.

The on-demand treatment of acute bleeds or breakthrough bleeds with NovoThirteen has not been studied in clinical trials.

As NovoThirteen contains a recombinant protein it may cause allergic reactions including anaphylactic reaction. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. If allergic or anaphylactic-type reactions occur, the administration should be immediately discontinued and further treatment with NovoThirteen should not be given.

Recombinant FXIII may contain trace amounts of yeast protein and therefore care should be taken when administering NovoThirteen to patients with known allergy to yeast.

Inhibitor formation
Inhibitor formation to NovoThirteen therapy has not been detected in clinical trials. Inhibitors may be suspected in the event of lack of therapeutic response observed as bleeding or demonstrated by laboratory findings including FXIII activity that fails to reach expected levels. In the event that inhibitors are suspected analysis for antibodies should be performed.

Patients known to have neutralising antibodies to FXIII should not be treated with NovoThirteen without close monitoring.

Thromboembolic risk
The reconstituted medicinal product must be handled in accordance with DOSAGE AND ADMINISTRATION. Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of activated rFXIII. Increased levels of activated rFXIII may increase the risk of thrombosis.

In case of predisposition to conditions of thrombosis, caution should be exercised due to the fibrin-stabilising effect of NovoThirteen. A stabilisation of the thrombus might occur, resulting in increased risk of vessel occlusions.

Effects on Fertility
The potential effect on fertility has not been studied in animals. No effects on reproductive organs have been seen in non-clinical studies.

Use in pregnancy
Category B2
There is no clinical data on the use of NovoThirteen in pregnant women. NovoThirteen has not been studied in pregnant animals. The risk to humans is not known. However, based on the therapeutic need, the use of NovoThirteen as replacement therapy may be considered during pregnancy.

Use in lactation
It is unknown whether rFXIII is excreted in human breast milk. The excretion of rFXIII drug substance in milk has not been studied in animals. A decision on whether to

continue/discontinue breast-feeding or to continue/discontinue therapy with NovoThirteen should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoThirteen therapy to the mother.

Paediatric use
Analyses of data from paediatric patients included in clinical trials have not identified difference in treatment response according to age.

Use in the Elderly
There is limited clinical experience administering NovoThirteen to elderly patients (≥65 yrs) with congenital FXIII deficiency.

Renal and Hepatic Impairment
Patients with hepatic impairment have not been studied. NovoThirteen may not be effective in patients with hepatic impairment if the hepatic impairment is severe enough to result in decreased levels of FXIII B-subunits. FXIII activity levels should be monitored in patients with severe hepatic impairment.

Patients with renal insufficiency requiring dialysis have not been studied in clinical trials.

Genotoxicity
Genotoxicity studies have not been performed with NovoThirteen since FXIII is an endogenous protein.

Carcinogenicity
No carcinogenicity studies have been conducted with NovoThirteen since FXIII is an endogenous protein.

Monitoring and Laboratory Tests
Monitoring NovoThirteen activity levels using a standard FXIII activity assay is recommended.

If during monitoring FXIII activity fails to reach expected levels or if reduced therapeutic effect is observed, analysis for antibodies should be performed.

INTERACTION WITH OTHER MEDICINES

There is no clinical data available on interaction between rFXIII and other medicinal products.

A potential synergistic effect of combined treatment with rFXIII and rFVIIa in an advanced cardiovascular model in cynomolgus monkey resulted in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

Based on the non-clinical study it is not recommended to combine rFXIII and rFVIIa.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

ADVERSE EFFECTS

In two phase 3 clinical trials, NovoThirteen has been administered to 41 patients with congenital factor XIII A-subunit deficiency (15 patients were between the age of 6 to less than 18 years old).

Tabulated list of adverse events
A total of 352 adverse events regardless of relationship to rFXIII were reported in the two phase 3 trials among 32 of the 41 patients receiving a total of 910 injections of rFXIII. Adverse events reported by more than 10% of the patients are presented in Table 2.

Table 2: Tabulated list of adverse events reported in more than 10% of patients

MedDRAa System Organ Class	Meddra Preferred Term	Number of patients	% of patients exposed	Number of events
General disorders and administration site conditions	Pyrexia	8	19.5	10
Infection and infestations	Nasopharyngitis	11	26.8	19
Injury poisoning and procedural complications	Excoriation	5	12.2	6
	Incorrect dose administration	5	12.2	12
	Joint sprain	5	12.2	7
Musculoskeletal and connective tissue disorders	Arthralgia	7	17.1	8
	Pain in extremity	7	17.1	7
Nervous system disorders	Headache	13	31.7	32
Respiratory, thoracic and mediastinal disorders	Nasal congestion	7	17.1	8
	Oropharyngeal pain	7	17.1	10

Tabulated list of adverse reactions

Frequency descriptions of all adverse reactions (assessed by the investigator to be possibly or probably related to rFXIII) identified from 41 patients with congenital FXIII deficiency exposed in phase 3 clinical trials are presented in the Table 3 (below), by system organ class. Within each grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse reactions reported in patients treated with rFXIII

Blood and lymphatic system disorders common (≥ 1/100 to < 1/10)	Leucopenia and aggravated neutropenia
Nervous system disorders common (≥ 1/100 to < 1/10)	Headache
Musculoskeletal and connective tissue disorders common (≥ 1/100 to < 1/10)	Pain in extremity
General disorders and administrative site conditions common (≥ 1/100 to < 1/10)	Injection site pain

Investigations	
common (≥ 1/100 to < 1/10)	Non- neutralising antibodies
common (≥ 1/100 to < 1/10)	Fibrin D dimer increased

Description of selected adverse reactions
One patient with a pre-existing neutropenia experienced a mild aggravation of neutropenia and leucopenia during treatment with NovoThirteen. Following discontinuation of NovoThirteen the patient's neutrophil count returned to levels similar to those prior to treatment with NovoThirteen.

Non-neutralising antibodies have been seen in 4 of the 41 exposed patients with congenital FXIII deficiency. The four events of non-neutralising antibodies occurred in patients below the age of 18 (age 8, 8, 14 and 16). These antibodies were seen at the start of treatment with NovoThirteen. All four patients received at least 2 doses of NovoThirteen. Three of the patients discontinued the study and returned to their previous treatment. One continued to receive NovoThirteen and the antibodies were no longer detected following repeated exposure. The antibodies had no inhibitory effect and the patients did not experience any adverse events or bleeding in association with these antibodies. Antibodies were transient in all patients.

One healthy subject developed binding antibodies after receiving the first dose of NovoThirteen. The antibodies had no inhibitory activity, and the subject did not experience any adverse events or bleeding in association with these antibodies. The antibodies were no longer detected at a 6-month follow up.

Paediatric population
In clinical studies, adverse reactions were more frequently reported in patients from 6 to less than 18 years of age than in adults. Adverse reactions were more frequently reported in patients aged from 6 to less than 18 years old than in adults. Three patients under 18 years experienced serious adverse reactions (non-neutralising antibodies) in comparison to no serious adverse reactions in patients over 18 years.

DOSAGE AND ADMINISTRATION
Treatment should be initiated and continued for a period of time under the supervision of a doctor experienced in the treatment of rare bleeding disorders. The congenital factor XIII A-subunit deficiency should be confirmed by appropriate diagnostic procedures.

For detailed instructions for reconstitution and administration of NovoThirteen, refer to the Instructions for Use leaflet.

Dose and dose interval
The recommended dose is 35 IU/kg body weight (bw) once monthly (every 28 days +/- 2 days), administered as an intravenous bolus injection. The dose volume in millilitres can be calculated from the formula below:

Dose volume in mL = 0.042 x subject bw (kg)

Dose adjustment can be considered necessary by the physician in certain situations where the prevention of bleeding is not appropriately covered by the recommended 35 IU/kg/month dose. This dose adjustment should be based on FXIII activity levels. Monitoring FXIII activity levels using a standard FXIII activity assay is recommended.

Low FXIII activity levels may indicate development of antibodies (refer to section Inhibitor development) in which case further treatment should only be performed under close patient supervision.

The amount of NovoThirteen is calculated upon body weight. When NovoThirteen is administered to small children a further dilution of the product might be necessary (see Special additional instructions for patients weighing less than 24 kg).

Special additional instructions for patients weighing less than 24 kg

If the body weight is less than 24 kg, the reconstituted NovoThirteen can be further diluted with 6.0 mL of 0.9% sodium chloride. To use the formula below the reconstituted product should be diluted with 6.0 mL of 0.9% sodium chloride.

Dose volume in mL of diluted product = 0.117 x Body weight in kilograms

The potency of this medicinal product is expressed in international units (IU).

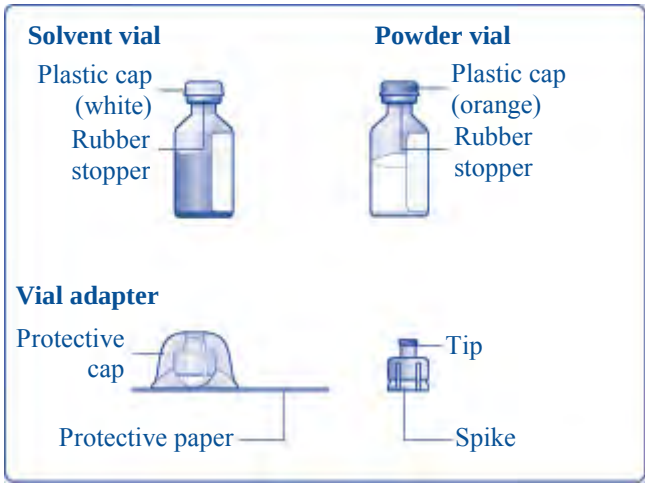
Monitoring NovoThirteen activity levels using a standard FXIII activity assay is recommended.

NovoThirteen User Instructions

To reconstitute and administer this medicinal product the following tools are needed: a 10 mL syringe or a syringe of convenient size according to the injection volume, alcohol swabs, the included vial adaptor and an infusion set (tubing, butterfly needle).

Preparing the solution

Wash the hands before starting. NovoThirteen powder and solvent vials should be at room temperature (not above 25°C) for reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use.

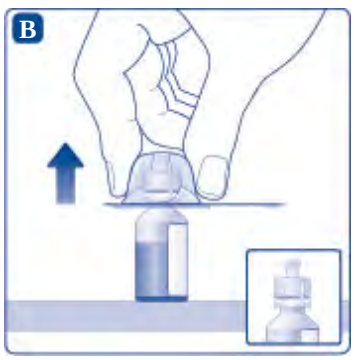


A

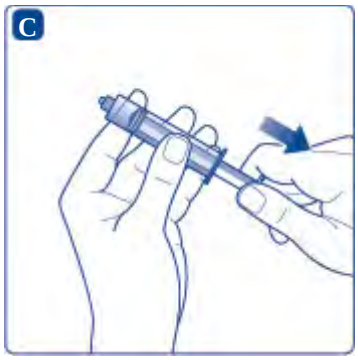
Remove the protective paper from the vial adaptor without taking it out of the protective cap. Attach the vial adaptor to the solvent vial (water for injection). Take care not to touch the spike on the vial adaptor.

B

Once attached, remove the protective cap from the vial adaptor by lightly squeezing the protective cap with your thumb and index finger as shown.

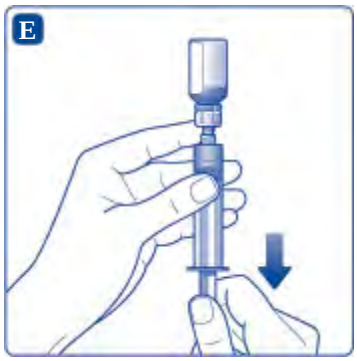


C
Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (mL equals cc on the syringe).

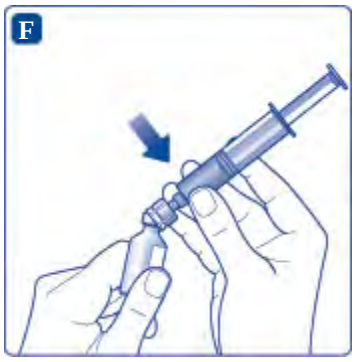


D
Screw the syringe securely onto the vial adaptor on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.

E
Hold the syringe with the solvent vial upside down. Pull the plunger to draw the solvent into the syringe.



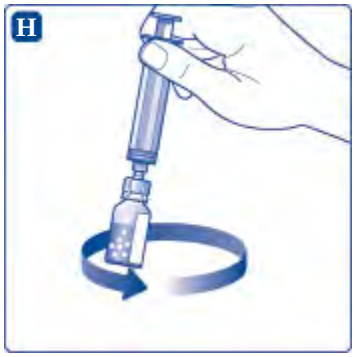
F
Remove the empty solvent vial by tipping the syringe with the vial adaptor.



G
Click the vial adaptor, still attached to the syringe, onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Do not aim the stream of solvent directly at the NovoThirteen powder as this may cause foaming. If foaming occurs, allow the foam to settle and then swirl gently before proceeding.

H
Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. If foaming occurs, allow the foam to settle and then swirl gently before proceeding.

Check the solution for visible particles and discolouration. If you notice either, do not use it. NovoThirteen reconstituted product is a clear, colourless solution. If a larger dose is needed, repeat the procedure in a separate syringe until the required dose if reached.

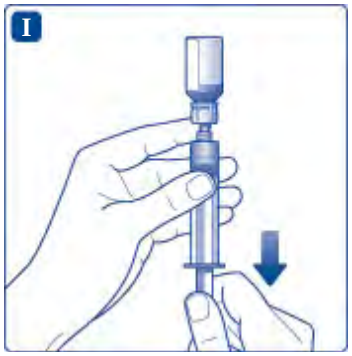


Important Information
Once you have prepared NovoThirteen for injection it should be used immediately. If the reconstituted product is not used immediately it should be used within 3 hours if stored at temperature below 25°C or within 24 hours if stored at 2 – 8°C. This is because if it is left longer, the medicine may no longer be sterile and the amount of activated rFXIII in NovoThirteen will increase. Activated NovoThirteen may increase the risk of getting a blood clot or it may increase the severity of a pre-existing blood clot.

Any unused product stored at room temperature for 3 hours, or stored in the refrigerator for longer than 24 hours, should be discarded.

The reconstituted product must not be frozen. If the reconstituted product does become frozen it must not be used and must be discarded.

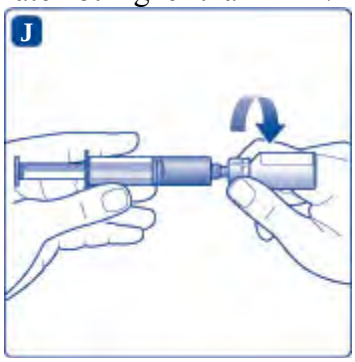
Injecting the solution
I
Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the vial). Hold the syringe with the vial upside down and pull the plunger to draw up the amount calculated for the injection into the syringe.



J
Unscrew the vial adaptor with the empty vial. NovoThirteen is now ready for injection in the vein. Follow the injection procedure as instructed by your healthcare professional.

The reconstituted NovoThirteen shall be administered as an intravenous bolus injection at a

rate not higher than 2 mL/minute.



K
Safely dispose of the syringe, vial adaptor, infusion set and vials. Any unused medicinal product and or waste materials should be disposed of in accordance with local requirements or as instructed by your healthcare professional.

Dilution of the reconstituted product with 0.9% sodium chloride
If dilution of the reconstituted NovoThirteen is necessary in order to be able to handle the dosing of children below 24 kg the reconstituted NovoThirteen should be diluted with 6.0 mL 0.9% sodium chloride (see section 'Special additional instructions for patients weighing less than 24 kg').

Ask your doctor for advice before the reconstituted NovoThirteen is diluted with 0.9% sodium chloride.

OVERDOSAGE

In reported cases of NovoThirteen overdose, a dose up to 2.3 times the recommended dose did not result in clinical symptoms being observed.

For further information on the management of overdose contact the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Storage Conditions

Store at 2-8°C. Refrigerate. Do not freeze. Store in the original package in order to protect from light. Do not use after the expiry date.

For storage conditions of the reconstituted product, see DOSAGE AND ADMINISTRATION

Presentation

Each NovoThirteen pack contains:

- a single use glass vial containing 2500 IU white, lyophilised powder for solution for injection
- a single use glass vial containing solvent (water for injection) for NovoThirteen for reconstitution, containing 3.2 mL
- a sterile vial adaptor for reconstitution

The glass vials are type 1 glass vials closed with a chlorobutyl (powder)/bromobutyl (diluent) rubber stopper sealed with a plastic disc and aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of plastic.

NAME AND ADDRESS OF THE SPONSOR

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

POISON SCHEDULE OF THE MEDICINE

Unscheduled.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

Date of first inclusion in the Australian Register of Therapeutic Goods: 7 November 2013

DATE OF MOST RECENT AMENDMENT

Not applicable.