

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoThirteen 2500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains catridecacog (recombinant coagulation factor XIII) (rDNA): 2500 IU per 3 ml, after reconstitution corresponding to a concentration of 833 IU/ml. The specific activity of NovoThirteen is approximately 165 IU/mg protein.

The active substance is produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white and the solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Long term prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.
Treatment of breakthrough bleeding episodes during regular prophylaxis.
NovoThirteen can be used for all age groups.

4.2 Posology and method of administration

Treatment should be initiated 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 including factor XIII activity and immunoassay and if applicable genotyping.

Posology

The potency of this medicinal product is expressed in international units (IU).
Although expressed in the same unit (IU), the posology of NovoThirteen is different from the dosing schedule of the other FXIII containing products (see section 4.4).

Prophylaxis

The recommended dose for prophylactic treatment is 35 IU/kg body weight once monthly (every 28 days \pm 2 days), administered as an intravenous bolus injection.

Treatment of bleeds

If a breakthrough bleed occurs during regular prophylaxis, it is recommended to treat with a single dose of 35 IU/kg body weight administered as an intravenous bolus injection.

If bleeds occur in a patient who is not on regular prophylaxis, a single dose of 35 IU/kg body weight as an intravenous bolus injection may be administered at the discretion of the treating physician in order to control the bleed (see section 4.4 'On-demand treatment').

Based on the actual concentration of NovoThirteen, the volume (in millilitres) to be administered to patients weighing at least 24 kg can be calculated from the formula below:

Dose volume in ml = 0.042 x subject body weight (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 NovoThirteen activity levels using a standard FXIII activity assay is recommended.

Minor surgery

It is recommended that minor surgery, including tooth extraction is done in connection with prophylactic dosing. Otherwise, an additional dose can be given if needed. The dose should be based on the FXIII activity levels.

Paediatric population

No dose adjustment is required when NovoThirteen is used in paediatric patients and the dose of 35 IU/kg body weight should be used for both prophylaxis and treatment of bleeds (see section 5.2 'Paediatric population').

However, if the paediatric patient weighs less than 24 kg, the reconstituted NovoThirteen should be further diluted with 6 ml of sodium chloride 0.9%, solution for injection to handle the dosing of small children (see section 6.6 'Special precautions for disposal and other handling – Use in the paediatric population').

The dose volume for small children can then be calculated by using the below formula:

Dose volume in ml = 0.117 x body weight in kilograms.

The calculation of the correction factor 0.117 is related to the exact quantity of the product and not the nominal value of the product.

Currently available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

Intravenous use.

The preparation should be administered immediately after reconstitution as a slow bolus intravenous injection at a rate not higher than 2 ml/minute, see section 4.4.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Considering that the posology and the FXIII concentration in NovoThirteen are different from those of the other FXIII containing products, careful attention should be paid to the calculation of the appropriate dose for the individual patient (see dose volume formula provided in section 4.2).

Traceability

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

Congenital FXIII B-subunit deficiency

In patients with FXIII deficiency, NovoThirteen is not effective if used for monthly 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 determined prior to treatment by appropriate diagnostic procedures including factor XIII activity and immunoassay and if applicable genotyping.

On-demand treatment

On-demand treatment of patients not on prophylactic treatment was not studied in clinical development programme.

Allergic reactions

As NovoThirteen contains a recombinant protein it may cause allergic reactions including anaphylactic reactions. 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.

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 which is 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 product must be handled in accordance with section 6.3.

Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of non-proteolytically activated NovoThirteen. Increased levels of activated NovoThirteen 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.

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.

Elderly patients

There is limited clinical experience in administering NovoThirteen to elderly patients with congenital FXIII deficiency.

Renal insufficiency

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

Sodium content

The medicinal product contains less than 1 mmol sodium (23 mg) per injection, indicating that it is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

There are no clinical data available on interaction between NovoThirteen and other medicinal products.

Based on the non-clinical study (see section 5.3) it is not recommended to combine NovoThirteen and recombinant activated FVII (rFVIIa).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies in pregnant women investigating drug associated risks. There are limited amount of data from the clinical use of NovoThirteen in pregnant women and available data do not show any negative effects on the health of the foetus/new-born child or for the pregnant woman. The use of NovoThirteen may be considered during pregnancy only if clearly indicated.

Animal reproduction studies have not been conducted with NovoThirteen (see section 5.3).

Breast-feeding

It is unknown whether rFXIII is excreted in human breast milk. The excretion of rFXIII 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.

Fertility

No effects on reproductive organs have been seen in non-clinical studies. There are no human data on potential effects on fertility.

4.7 Effects on ability to drive and use machines

NovoThirteen has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction is 'headache' reported in 37% of patients.

Tabulated list of adverse reactions

In clinical trials, NovoThirteen has been administered to 82 patients with congenital factor XIII A-subunit deficiency (3112 doses of NovoThirteen).

Frequency descriptions of all adverse reactions identified from 82 patients with congenital FXIII deficiency exposed in clinical trials are presented in the below table by system organ class.

Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<i>Blood and lymphatic system disorders</i>	
Common ($\geq 1/100$ to $< 1/10$)	Leucopenia and aggravated neutropenia
<i>Nervous system disorders</i>	
Common ($\geq 1/100$ to $< 1/10$)	Headache
<i>Musculoskeletal and connective tissue disorders</i>	
Common ($\geq 1/100$ to $< 1/10$)	Pain in extremity
<i>General disorders and administration site conditions</i>	

Common ($\geq 1/100$ to $< 1/10$)	Injection site pain
<i>Investigations</i>	
Common ($\geq 1/100$ to $< 1/10$)	Non-neutralising antibodies
Common ($\geq 1/100$ to $< 1/10$)	Fibrin D-dimer increased

Description of selected adverse reactions

One patient with 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 82 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 4 patients received at least 2 doses of NovoThirteen. 3 of the patients discontinued the study and returned to their previous treatment. One continued to receive rFXIII and the antibodies decreased below detection limit. The antibodies had no inhibitory action 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 low-titer, transient non-neutralising 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 disappeared in the 6-month follow up.

In all cases, the non-neutralising antibodies were found to be of no clinical significance.

In a post-authorisation safety study transient non-neutralising antibodies were seen in a child with congenital FXIII deficiency after several years of treatment with NovoThirteen. No clinical findings were associated with these antibodies.

Paediatric population

21 patients were between the age of 6 to less than 18 years old and 6 patients were less than 6 years old (total of 986 exposures of NovoThirteen in paediatric subjects (less than 18 years old).

In clinical studies, adverse reactions were more frequently reported in patients aged from 6 to less than 18 years old than in adults. 3 patients (14%) aged between 6 and 18 years experienced serious adverse reactions in comparison to 0 patients over 18 years that experienced serious adverse reactions. Four cases of non-neutralising antibodies were reported at the start of the treatment in patients from 6 to 18 years of age. 3 of these patients discontinued the study due to the adverse reaction.

In patients below 6 years, no anti-rFXIII antibodies, no thromboembolic adverse events or other safety issues were reported.

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

In the reported cases of NovoThirteen overdose up to 2.3 times, no clinical symptoms have been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihæmorrhagics, Blood Coagulation factor, ATC code: B02BD11.

Mechanism of action

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 a carrier molecule for the FXIII A-subunit in circulation, and is present in excess in plasma. When the FXIII A-subunit is bound to the 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.

NovoThirteen is a recombinant coagulation factor XIII A-subunit produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. It is structurally identical to the human FXIII A-subunit [A_2]. NovoThirteen (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].

Pharmacodynamic effects

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.

NovoThirteen has been shown to have the same pharmacodynamic properties in plasma as endogenous FXIII.

Clinical efficacy and safety

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 rFXIII 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 \pm 2 days). Five bleeding episodes requiring treatment with a FXIII-containing product have been observed in four patients during treatment with rFXIII in the trial.

The mean rate of treatment-requiring bleeds was determined to 0.138 per subject year. In the primary endpoint analysis covering the referred period, 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 for the 41 patients).

In the F13CD-1725 extension trial F13CD-3720, the age-adjusted rate of bleeds that required treatment with a FXIII-containing product was estimated to be 0.021 bleeds per subject year with a 95% CI of [0.0062; 0.073] (model-based estimate corresponding to a mean age of the trial population of 31.0 years).

The crude bleeding rates in the two trials, F13CD-1725 and F13CD-3720, not adjusted for age, were 0.138 and 0.043 respectively, corresponding to a total of 13 bleeds over 223 subject-years and a pooled rate of 0.058.

A 6 year post-authorisation safety study NN1841-3868 including 30 patients with FXIII A-subunit deficiency was conducted to investigate the long term safety of rFXIII. No safety concerns were

identified. Five traumatic bleeding episodes in four patients were treated with rFXIII during prophylaxis.

The mean rate of bleeding episodes requiring treatment with FXIII was 0.066 bleeds per patient per year (95% CI: 0.029 - 0.150).

Minor surgeries

Six patients had a total of 9 minor surgeries during the post-authorisation safety study NN1841-3868. Seven of the 9 minor surgery cases took place 0-3 days after last prophylactic dose of rFXIII and rFXIII was given post-surgery in 1 case. In the latter 2 of the 9 cases, the last prophylactic dose was given 12-15 days before surgery, and an extra single dose of rFXIII at 23.2 IU/kg and 21.4 IU/kg respectively was given prior surgery. In 8 of the 9 cases the haemostatic response was reported as good or excellent. Outcome was not reported for the last case.

In trial F13CD-3720, extension trial to the pivotal phase 3 trial F13CD-1725, 12 minor surgeries were performed in 9 patients. All surgeries took place within 1-21 days after the last prophylactic dose of rFXIII. No additional doses were given. The outcome in all 12 cases was favourable.

Paediatric population

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

Twenty-one children between the age of 6 to less than 18 years old and six children less than 6 years old have been treated with NovoThirteen for a total of 986 exposures.

Children above 6 years were investigated through the pivotal phase 3 trial (F13CD-1725) and the extension study (F13CD-3720) assessing the safety of monthly replacement therapy with NovoThirteen.

The 6 patients below 6 years were investigated through a single dose pharmacokinetic phase 3b trial (F13CD-3760) and then, included in the long-term follow-up trial (F13CD-3835) assessing the safety and the efficacy of monthly replacement therapy with NovoThirteen. No treatment requiring bleeding episodes have been detected in patients below 6 years during 17 years of cumulative follow-up, representing a total of 214 doses. The suggested dose of 35 IU/kg has shown to be appropriate to provide haemostatic coverage in this young population.

In the post-authorisation safety study NN1841-3868, 13 children under 18 years were enrolled. Overall, no differences in treatment response or safety profile were seen in the paediatric population compared to the adult population.

5.2 Pharmacokinetic properties

The steady-state pharmacokinetics (PK) of NovoThirteen has been assessed in patients with congenital FXIII A-subunit deficiency after dosing 35 IU/kg NovoThirteen i.v. every 4th week. The PK parameters are based on FXIII activity measured by the Berichrom assay. The PK parameters are summarised in the below table.

Steady-state PK parameters Geometric mean (range)	Trial F13CD-3720
Number of subjects	23
Age (years)	30.7 (7-58)
Gender	5F+18M

C _{max} (IU/ml)	0.87 (0.57-1.24)
C _{28days} (IU/ml)	0.16 (0.03-0.32)
AUC _{0-inf} (IU*h/ml)	318.1 (223.1-515.1)
CL (ml/h/kg)	0.15 (0.10-0.21)
V _{ss} (ml/kg)	70.8 (44.0-150.3)
t _½ (days)	13.7 (10.1-24.6)
MRT (h)	478 (344-1028)

C_{max}: maximum plasma concentration

C_{28days}: plasma concentration 28 days after administration

AUC_{0-inf}: area under the concentration-time curve from time of administration to infinity

CL: clearance

V_{ss}: apparent volume of distribution

t_½: terminal elimination half-life

MRT: mean residence time

Paediatric population

The single-dose PK of NovoThirteen has been investigated in 6 children below 6 years of age with congenital FXIII A-subunit deficiency after a single iv dose of 35 IU/kg. The PK parameters are presented in the below table.

Single-dose PK parameters Geometric mean (range)	Trial F13CD-3760 Paediatric patients
Number of subjects	6
Age (years)	2.7 (1-4)
Gender	3F+3M
C _{max} (IU/ml)	0.67 (0.49-0.91)
C _{30days} (IU/ml)	0.21 (0.05)#
AUC _{0-inf} (IU*h/ml)	355.1 (285.3-425.6)
CL (ml/h/kg)	0.15 (0.13-0.17)
V _{ss} (ml/kg)	85.7 (49.3-143.0)
t _½ (days)	15.0 (9.8-24.8)
MRT (h)	575 (383-871)

Mean (SD)

C_{\max} : maximum plasma concentration
 $C_{30\text{days}}$: plasma concentration 30 days after administration
 $AUC_{0-\infty}$: area under the concentration-time curve from time of administration to infinity
CL: clearance
 V_{ss} : apparent volume of distribution
 $t_{1/2}$: terminal elimination half-life
MRT: mean residence time

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology and repeated dose toxicity. All findings in the non-clinical safety programme have been related to expected exaggerated pharmacology (general thrombosis, ischaemic necrosis and ultimately mortality) of rFXIII and non-proteolytically activated recombinant FXIII at dose levels in excess (> 48 fold) of the maximum recommended clinical dose of 35 IU/kg.

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.

Animal reproductive or developmental toxicity studies have not been performed. No effects on reproductive organs were noted in the repeated dose toxicity studies.
Genotoxic potential or carcinogenicity has not been studied since rFXIII is an endogenous protein.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Sodium chloride
Sucrose
Polysorbate 20
L-histidine
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

Solvent:

Water for injections

6.2 Incompatibilities

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

Following reconstitution the product should be administered separately and not mixed with infusion solutions nor be given in a drip.

6.3 Shelf life

2 years.

After reconstitution, the medicinal product should be used immediately due to the risk of microbiological contamination.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).

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

Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder (2500 IU) in a vial (glass type I) with rubber stopper (chlorobutyl) and 3.2 ml solvent in a vial (glass type I) with rubber stopper (bromobutyl) and a vial adapter for reconstitution.

Pack size of 1.

6.6 Special precautions for disposal and other handling

NovoThirteen user instructions

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

Preparing the solution

Always use an aseptic technique. Before starting, the hands should be washed. Bring the powder and solvent vials to a temperature not above 25°C by holding them in the hands. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use.

The product is reconstituted using the vial adapter included.

Attach the vial adapter to the solvent vial (water for injections). Take care not to touch the spike on the vial adapter.

Pull the plunger to draw in a volume of air equal to the total amount of solvent in the solvent vial.

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

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

Remove the empty solvent vial by tipping the syringe with the vial adapter.

Click the vial adapter, still attached to the syringe onto the powder vial. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the powder as this will cause foaming.

Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. NovoThirteen should be inspected visually for extraneous (for any foreign) particulate matter and discoloration prior to administration. In the event of either being observed, discard the medicinal product.

Reconstituted NovoThirteen is a clear, colourless solution.

If a larger dose is needed, repeat the procedure in a separate syringe until the required dose is reached.

If the patient weighs less than 24 kg, the reconstituted NovoThirteen should be diluted with 6 ml of sodium chloride 0.9%, solution for injection (refer to the section Use in the paediatric population for further detailed instructions on the dilution step).

Important information

Once prepared, NovoThirteen for injection should be used immediately.

Injecting the solution

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.

Unscrew the vial adapter with the vial.

The product is now ready for injection.

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

Use in the paediatric population

Dilution of the reconstituted product with sodium chloride 0.9%, solution for injection

If the paediatric patient weighs less than 24 kg, the reconstituted NovoThirteen should be diluted with 6 ml of sodium chloride 0.9%, solution for injection to be able to handle the dosing of small children (see section 4.2 'Posology and method of administration – Paediatric population').

To dilute the reconstituted NovoThirteen the following tools are needed: a vial containing sodium chloride 0.9%, solution for injection, a 10 ml syringe and alcohol swabs.

General instructions for dilution

The dilution should be performed in accordance with aseptic rules.

Carefully draw exactly 6 ml sodium chloride 0.9%, solution for injection, into the 10 ml syringe.

Slowly inject the 6 ml sodium chloride 0.9%, solution for injection, into the reconstituted NovoThirteen vial.

Gently swirl the vial to mix the solution.

The diluted solution is a clear, colourless solution. Check the injection solution for particulate matter and for discolouration. If either is noticed, please discard.

After dilution proceed to the step 'Injecting the solution'.

Any residual material of the diluted product has to be discarded immediately.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/12/775/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 September 2012

Date of latest renewal: 24 May 2017

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE(S) AND MANUFACTURER(S) 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
Novo Allé
DK-2880 Bagsværd
Denmark

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

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Allé
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 within 60 days as a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

NovoThirteen 2500 IU powder and solvent for solution for injection
catridecacog (rDNA factor XIII)

2. STATEMENT OF ACTIVE SUBSTANCE

One vial contains catridecacog (recombinant coagulation factor XIII) (rDNA) 2500 IU per 3 ml, after reconstitution corresponding to a concentration of 833 IU/ml.

3. LIST OF EXCIPIENTS

Powder: Sodium chloride, sucrose, polysorbate 20, L-histidine, hydrochloric acid, sodium hydroxide
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

2500 IU powder in a vial,
3.2 ml solvent in a vial,
1 vial adapter

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use
Read the package leaflet before use

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
After reconstitution, use the medicine immediately due to the risk of microbiological contamination.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Store in the original package in order to protect from light.
Do not freeze.

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/1/12/775/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoThirteen

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**Label for powder vial****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

NovoThirteen 2500 IU
powder for injection
catridecacog
IV use after reconstitution

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2500 IU

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for solvent vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoThirteen
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
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3.2 ml

6. OTHER

For reconstitution

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NovoThirteen 2500 IU powder and solvent for solution for injection

catridecacog (recombinant coagulation factor XIII)

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 NovoThirteen is and what it is used for
2. What you need to know before you use NovoThirteen
3. How to use NovoThirteen
4. Possible side effects
5. How to store NovoThirteen
6. Contents of the pack and other information.

1. What NovoThirteen is and what it is used for

What NovoThirteen is

NovoThirteen contains the active substance catridecacog, which is identical to human coagulation factor XIII, an enzyme necessary for blood clotting. NovoThirteen replaces the missing factor XIII and helps to stabilise the initial blood clot by producing a mesh around the clot.

What NovoThirteen is used for

NovoThirteen is used to prevent bleeding in patients who do not have enough or are missing part of factor XIII (that is called A-subunit).

2. What you need to know before you use NovoThirteen

It is important that you use NovoThirteen for injection immediately after preparation.

Do not use NovoThirteen

- If you are allergic to catridecacog or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, ask your doctor before using this medicine.

Warnings and precautions

Talk to your doctor before using NovoThirteen:

- If you have or have ever had a higher risk of blood clots forming (thrombosis), as NovoThirteen may increase the severity of a pre-existing blood clot.
- If you have or have ever had liver damage.

Contact your doctor immediately:

- If you experience bleeding during your treatment with NovoThirteen occurring spontaneously and/or requiring treatment.

- If you experience an allergic reaction to NovoThirteen. The signs may include: hives, itching, swelling, difficulty breathing, low blood pressure (signs include paleness and coldness of skin, rapid heartbeat), feeling dizzy and sweating.

Other medicines and NovoThirteen

Tell your doctor if you are using, have recently used or might use any other medicines.

It is not recommended to use NovoThirteen and recombinant coagulation factor VIIa (another blood clotting factor) together.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, or if you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

NovoThirteen contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially 'sodium-free'.

3. How to use NovoThirteen

Your treatment with NovoThirteen should be initiated by a doctor experienced in the treatment of rare bleeding disorders.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Before you can use NovoThirteen for injection you need to reconstitute the product. Please see NovoThirteen user instructions.

NovoThirteen is given as an injection into a vein. Your dose will depend on your body weight. The usual dose for prevention of bleeds is 35 IU for each kilogram of body weight. The injections are given once a month (every 28 ± 2 days).

If you experience a bleed, you should contact your doctor who will decide if an injection is needed. NovoThirteen should be injected at a rate not higher than 2 ml/minute.

Based on the concentration of NovoThirteen solution, the dose volume to be injected (in millilitres) can be calculated from this formula:

Dose volume in millilitres = $0.042 \times$ your body weight in kilograms.

You should only use the prescribed dose calculated by your doctor from this formula considering that the usual dose and the concentration of NovoThirteen are different from those of the other products which contain factor XIII.

Your doctor may adapt the dose if this is deemed necessary.

Use in small children

For children weighing less than 24 kg the reconstituted NovoThirteen should be further diluted with 6 ml of sodium chloride 0.9%, solution for injection to be able to handle the dosing of small children. For more information see section 'NovoThirteen user instructions – Instructions of how to dilute the reconstituted NovoThirteen'.

The dose volume for the reconstituted NovoThirteen diluted with 6 ml sodium chloride 0.9%, solution for injection can be calculated from this formula:

Dose volume in millilitres = $0.117 \times$ body weight in kilograms.

Use in children and adolescents (weighing more than 24 kg)

NovoThirteen can be used in children and adolescents in the same way as in adults for both prevention of bleeds and if you experience a bleed.

If you use more NovoThirteen than you should

There is limited information on overdose with NovoThirteen. None of the reported cases have shown any signs of illness. Contact your doctor if you have injected more NovoThirteen than you have been instructed.

If you forget to use NovoThirteen

If you forget an injection of NovoThirteen, talk to your doctor. Do not take a double dose to make up for a forgotten dose.

If you stop using NovoThirteen

If you stop using NovoThirteen, you are not protected against bleeding. Do not stop using NovoThirteen without talking to your doctor. Your doctor will explain what might happen if you stop treatment and discuss other options with you.

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.

Side effects include:

Common (may affect up to 1 in 10 people):

- Headache (most common side effect)
- Pain where the injection is given
- Pain in the legs and arms
- Increased amount of small protein fragments caused by break down of blood clots
- A drop in the number of some types of white blood cells. This means your body may be more prone to infections
- Development of antibodies against factor XIII which have no influence on the effect of the drug.

Side effects in children:

The side effects observed in children are the same as also observed in adults but the side effects may be more common in children than in adults.

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 NovoThirteen

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

Do not use this medicine after the expiry date which is stated on the label and the outer carton after 'EXP.'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C).

Do not freeze.

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

Once prepared, NovoThirteen for injection should be used immediately.

The solution is clear and colourless. Do not use this medicine if there are particles in it or it is discoloured when reconstituted.

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 NovoThirteen contains

- The active substance is catridecacog (recombinant coagulation factor XIII: 2500 IU/3 ml, after reconstitution, corresponding to a concentration of 833 IU/ml.
- The other ingredients are for the powder sodium chloride, sucrose and polysorbate 20, L-histidine, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH adjustment) and for the solvent water for injections.

What NovoThirteen looks like and contents of the pack

NovoThirteen is supplied as a powder and solvent for solution for injection (2500 IU powder in a vial and 3.2 ml solvent in a vial, with a vial adapter).

Pack size of 1.

The powder is white and the solvent is clear and colourless.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

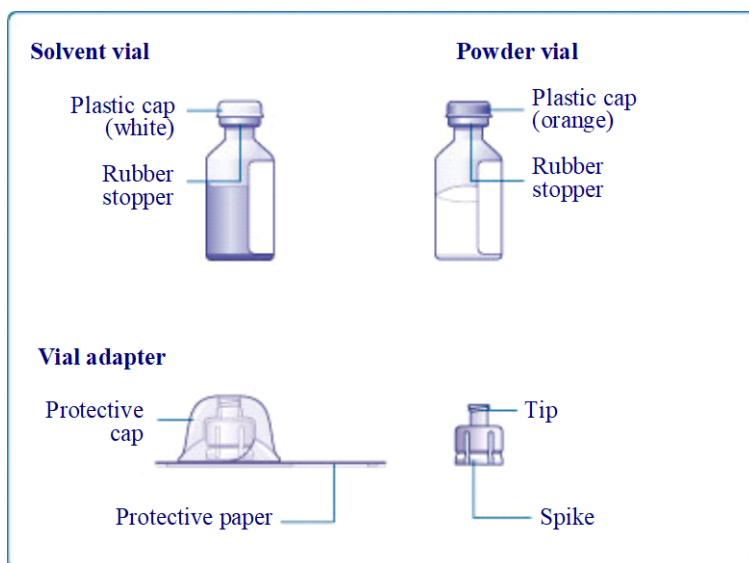
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

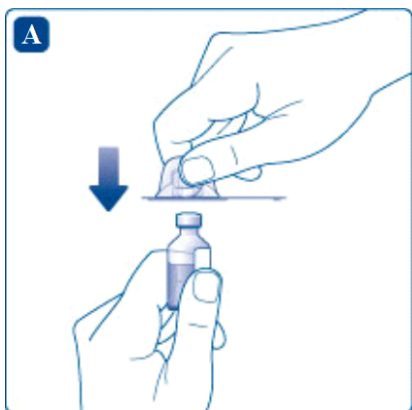
NovoThirteen user instructions

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



Preparing the solution

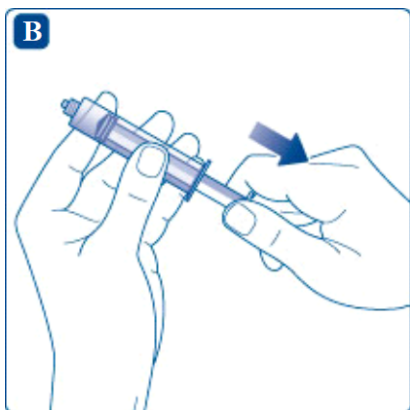
Always use an aseptic technique. Before starting, the hands should be washed. Bring the powder and solvent vials to a temperature not above 25°C, by holding them in the hands until they feel as warm as your hands. Remove the plastic caps from the 2 vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use.



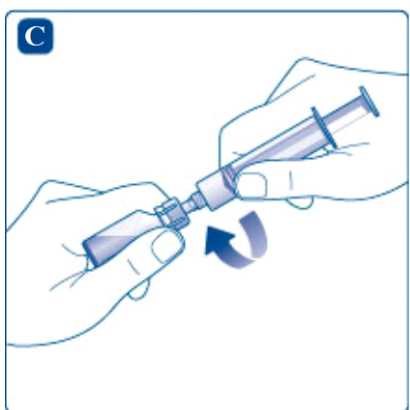
The product is reconstituted using the vial adapter included.

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

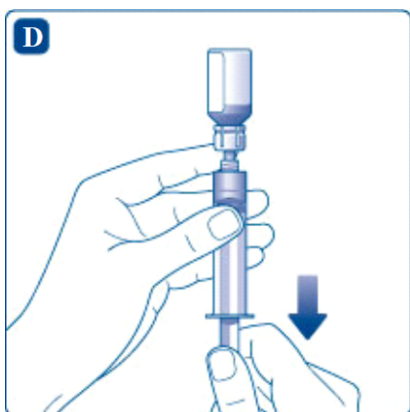
Once attached, remove the protective cap from the vial adapter.



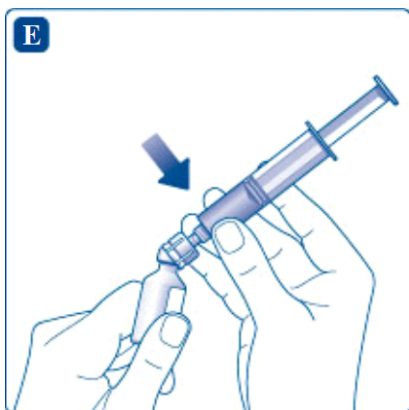
Pull the plunger to draw in a volume of air equal to the total amount of solvent in the solvent vial.



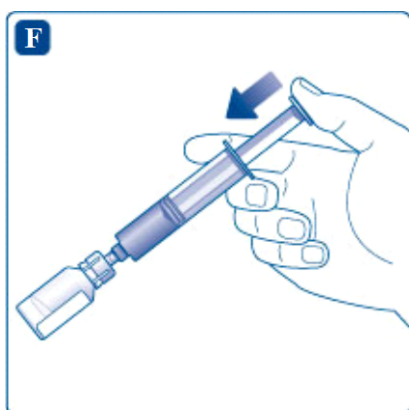
Screw the syringe tightly onto the vial adapter on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.



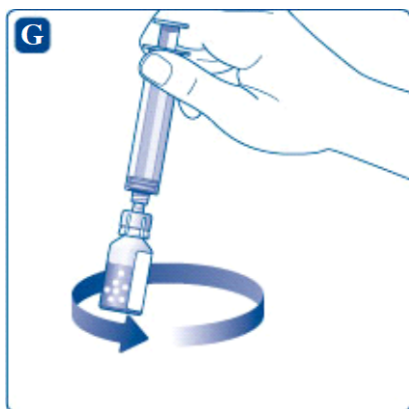
Hold the syringe with the solvent vial upside down. Pull the plunger to draw the solvent into the syringe.



Remove the empty solvent vial by tipping the syringe with the vial adapter.



Click the vial adapter, 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. Make sure not to aim the stream of solvent directly at the powder as this will cause foaming.



Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

NovoThirteen should be inspected visually for extraneous (for any foreign) particulate matter and discoloration prior to administration. In the event of either being observed, discard the medicinal product.

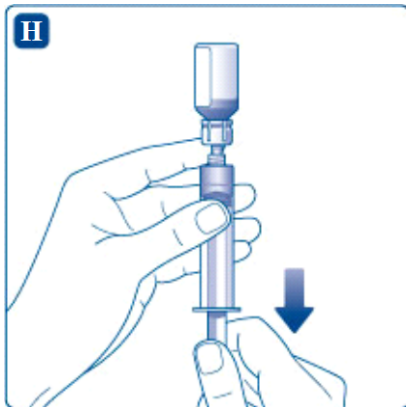
Reconstituted NovoThirteen is a clear, colourless solution.

If a larger dose is needed, repeat the procedure in a separate syringe until the required dose is reached.

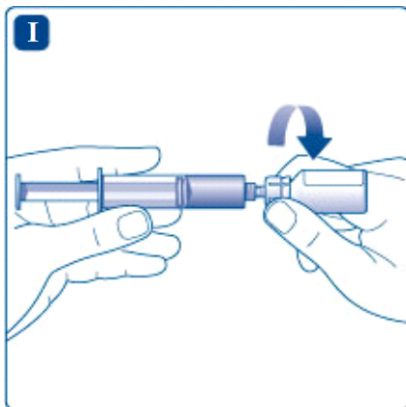
Important information

Once prepared, NovoThirteen for injection should be used immediately.

In case a dilution of the reconstituted NovoThirteen is needed proceed to the section ‘Dilution of the reconstituted product with sodium chloride 0.9%, solution for injection’.



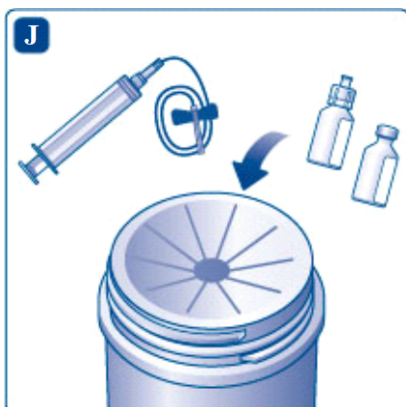
Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the vial). Hold the syringe with the vial upside down and pull the plunger to draw the amount calculated for the injection.



Unscrew the vial adapter with the vial.

The product is now ready for injection in the vein. Follow the injection procedure as instructed by your doctor.

After the injection



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

Instructions of how to dilute the reconstituted NovoThirteen

To dilute the reconstituted NovoThirteen the following tools are needed: a vial containing sodium chloride 0.9%, solution for injection, a 10 ml syringe and alcohol swabs.

General instructions for dilution

The dilution should be performed in accordance with aseptic rules.

Carefully draw exactly 6 ml sodium chloride 0.9%, solution for injection, into the 10 ml syringe.

Slowly inject the 6 ml sodium chloride 0.9%, solution for injection, into the reconstituted NovoThirteen vial.

Gently swirl the vial to mix the solution.

The diluted solution is a clear, colourless solution. Check the injection solution for particulate matter and for discolouration. If either is noticed, please discard.

After dilution proceed to step H.

Any residual material of the diluted product has to be discarded immediately.

In case of any questions ask your doctor or nurse.