

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

NovoThirteen 2500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally 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.

*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 prophylactic treatment of bleeding in adult and paediatric patients with congenital factor XIII A-subunit deficiency.

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 unitage (IU), the posology of NovoThirteen is different from the dosing schedule of the other FXIII containing products (see section 4.4).

The recommended dose is 35 IU/kg body weight (bw) once monthly (every 28 days +/- 2 days), administered as an intravenous bolus injection. Based on the actual concentration of NovoThirteen, the dose 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 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 NovoThirteen activity levels using a standard FXIII activity assay is recommended.

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 (see section 5.2 'Paediatric population').

However, if the paediatric patient weighs less than 24 kg, the reconstituted NovoThirteen should be diluted with 6.0 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 the reconstituted NovoThirteen diluted with 6.0 ml sodium chloride 0.9% solution for injection can 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 section 4.8, 5.1 and 5.2.

Method of administration

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

The preparation should be administered as a slow bolus intravenous injection at a rate not higher than 2 ml/minute.

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

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.

The on-demand treatment of acute bleeds or breakthrough bleeds with NovoThirteen has not been studied in clinical trials. An alternative treatment should be considered in such situations.

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).

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 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.

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.

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

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

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 rFVIIa.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no clinical data on the use of NovoThirteen in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3) as 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 a replacement therapy may be considered during pregnancy.

Breast-feeding

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.

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

In clinical trials, NovoThirteen has been administered to 56 patients with congenital factor XIII A-subunit deficiency (1043 doses of NovoThirteen). 15 patients were between the age of 6 to less than 18 years old and 6 patients were less than 6 years old (total of 393 exposures of NovoThirteen in paediatric subjects (less than 18 years old).

The most frequent adverse reaction is “headache” reported in 34 % of patients.

Tabulated list of adverse reactions

Frequency descriptions of all adverse reactions identified from 51 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 56 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.

Paediatric population

In clinical studies, adverse reactions were more frequently reported in patients aged from 6 to less than 18 years old than in adults. 4 patients (25%) aged between 6 and 18 years experienced serious adverse reactions in comparison to 3 patients over 18 years (8.5%) 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: Antihemorrhagics Blood Coagulation factor XIII, ATC code: B02BD11.

Mechanism of action

In plasma, FXIII circulates as a heterotetramer [A₂B₂] 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 [A₂B₂], the half-life of the FXIII A-subunit [A₂] 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 [A₂]. NovoThirteen (A-subunit) binds to free human FXIII B-subunit resulting in a heterotetramer [rA₂B₂] with a similar half-life to endogenous [A₂B₂].

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 +/- 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 0.151 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 0.053/year (95% CI: 0.010 - 0.272; model-based estimate corresponding to the mean age of 26.4 years for the 41 patients).

Paediatric population

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

Fifteen 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 393 exposures.

Children above 6 years were investigated through the pivotal phase 3 trial (F13CD-1725) and the on-going 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 on-going 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 8.7 years of cumulative follow-up, representing a total of 116 doses. The suggested dose of 35 IU/kg has shown to be appropriate to provide haemostatic coverage in this young population.

5.2 Pharmacokinetic properties

Based on FXIII activity as measured by the Berichrom assay for 471 monthly doses of rFXIII, a half-life of rFXIII of 11.8 days was estimated in patients with congenital FXIII deficiency. This is in agreement with the elimination pharmacokinetics estimated from a clinical pharmacology trial in healthy subjects, which determined the half-life to be 11.8 days. In this trial the mean volume of distribution at steady state was 47 ml/kg, mean residence time was 15.5 days and mean clearance was 0.13 mL/kg.

Paediatric population

In a pharmacokinetic trial 6 children (age 1 to less than 6 years old) with congenital FXIII A-subunit deficiency were exposed to one single i.v. dose of NovoThirteen 35 IU/kg. The mean $t_{1/2}$ of FXIII was approximately 15 days (range: 10 to 25 days). In this trial, the mean clearance in children was 0.15 ml/h/kg.

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.

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 6.0 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 6.0 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 6.0 ml sodium chloride 0.9%, solution for injection, into the 10 ml syringe. Slowly inject the 6.0 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 discoloration. 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

10. DATE OF REVISION OF THE TEXT

January 2014

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
Hagedornsvej 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**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed Risk Management Plan 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, a letter is sent to all expected and actual prescribers of NovoThirteen with an Educational Pack containing the following:

1. Physician brochure
2. Patient brochure

Both documents are to be used as part of an educational plan aiming to minimise risks of medication errors, risk of thromboembolic events due to increased levels of non-proteolytically activated rFXIII in connection with incorrect storage, and risk of off-label use for treatment of breakthrough bleeding. The MAH should ensure harmonisation between terminology used in the brochures and the product information.

The physician brochure should contain the following key elements and item:

- Indication of the product
- The risks of off-label use within FXIII congenital deficiency
- Appropriate diagnostic procedures to confirm FXIII A-subunit deficiency
- Warning of the difference of both posology and concentration between NovoThirteen and other FXIII containing products (The recommended dose of NovoThirteen is 35 IU/kg body weight (bw) once monthly, administered as an intravenous bolus injection. The dose volume in millilitres should be calculated based on body weight for each patient using the following formula: Dose volume in ml = 0.042 x subject bw (kg) if bw > 24 kg or dose volume in ml = 0.117 x bw (kg) if bw < 24 kg).
- Correct handling and the risks associated with mishandling
- Embolic and thrombotic events including the increased risk of vessel occlusion in patients at risk of thrombosis
- What to do in the event of incorrect storage, thrombosis or embolism
- Contraindication of hypersensitivity
- Warning and precautions regarding anaphylaxis
- The importance of collecting safety data and how to enrol patients in the PASS and other registries
- Distribution and use of the patient brochure and the need to ensure that the patient has read and understood the brochure
- Summary of Product Characteristics.

The patient brochure, to be distributed to patients by the prescribers, should contain the following key elements and item:

- Indication of the product
- The risks of off-label use within FXIII congenital deficiency
- How to safely store, handle, reconstitute and administer the product
- The risks associated with incorrect storage and mishandling
- How to recognise the potential side effects (thrombosis and embolism)
- What to do in the event of incorrect storage, thrombosis or embolism
- Package Leaflet.

The Marketing Authorisation Holder must implement this educational plan nationally, prior to marketing. The final content, format and distribution modalities of both documents should be agreed with the national competent authority in each Member State.

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 nominally 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 (for pH-adjustment), sodium hydroxide (for pH-adjustment)
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, the medicinal product should be used immediately due to the risk of microbiological contamination.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
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

Any unused product or waste material should be disposed of in accordance with local requirements

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

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NovoThirteen

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
Intravenous 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

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

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.2 ml water for injections

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)

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

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

What is in this leaflet:

1. What 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.

What NovoThirteen is used for

NovoThirteen is used to prevent bleeding in patients who do not have enough factor XIII.

NovoThirteen replaces the missing factor XIII and helps to stabilise the initial blood clot by producing a mesh around the clot.

2. What you need to know before you use NovoThirteen

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. In this last case your doctor will prescribe an alternative treatment to treat the bleeding.
- If you experience an allergic reaction to recombinant blood coagulation factor XIII. 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

The use of NovoThirteen may be necessary during 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 medicinal product 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.

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

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 x your body weight in kg.

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

Dilution of the reconstituted product with 6 ml sodium chloride 0.9%, solution for injection

If NovoThirteen is injected into a child weighing less than 24 kg the reconstituted NovoThirteen should be diluted with 6.0 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 - Dilution of the reconstituted product with sodium chloride 0.9%, solution for injection'.

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

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

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

The reconstituted NovoThirteen should be injected at a rate not higher than 2 ml/minute.

For more information on how to get your injection ready, see ‘NovoThirteen User Instructions’.

Use in children and adolescents

NovoThirteen can be used in children and adolescents in the same way as in adults.

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 non-neutralising factor XIII antibodies which have no influence on the effect of the active substance.

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.

* produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology.

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

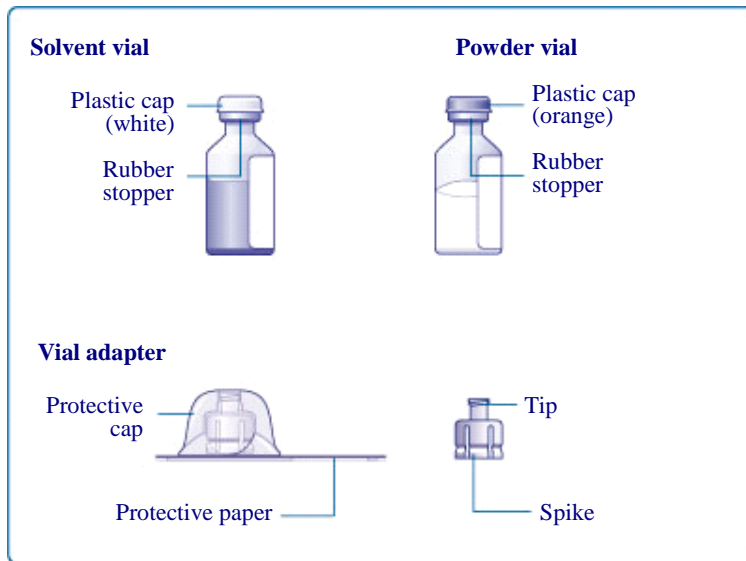
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

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>

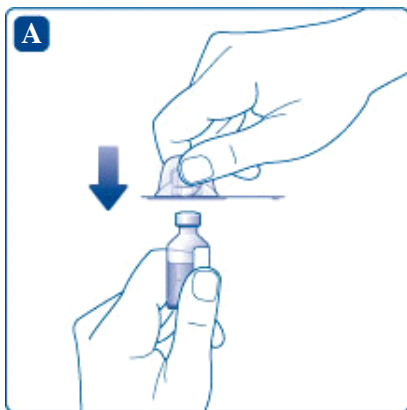
NovoThirteen user instructions

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

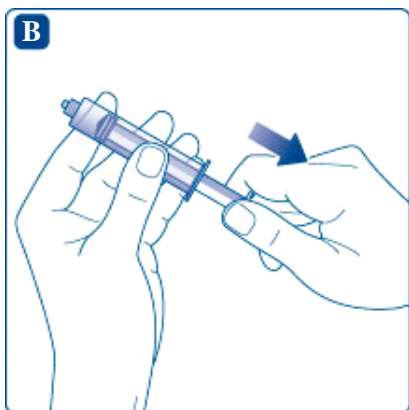
Always use an aseptic technique. Before starting, the hands should be washed. Bring the powder and solvent vials to a temperature not above 25°C, by holding them in the hands until they feel as warm as your hands. Remove the plastic caps from the 2 vials. If the caps are loose or missing, do not use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



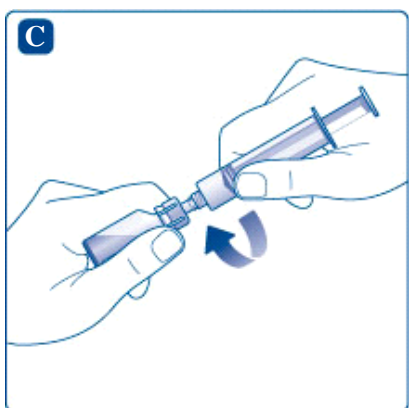
The product is reconstituted using the vial adapter included.

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.

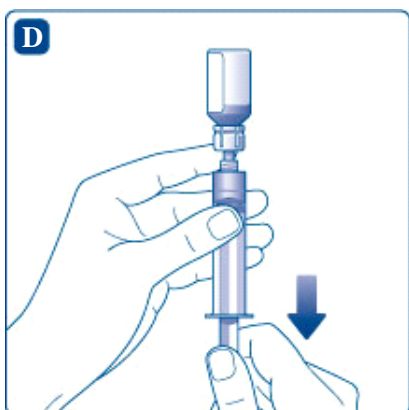
Once attached, remove the protective cap from the vial adapter .



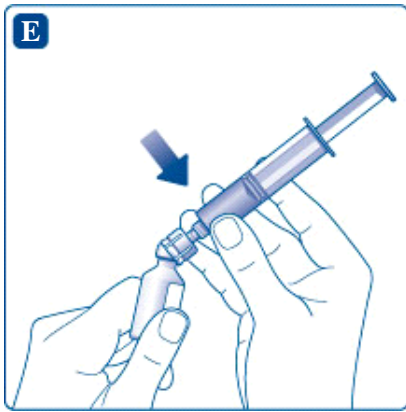
Pull the plunger to draw in a volume of air equal to the total amount of solvent in the solvent vial.



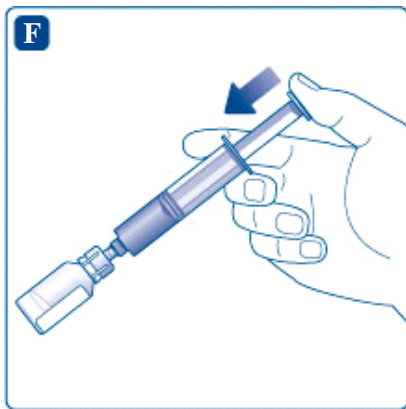
Screw the syringe tightly onto the vial adapter on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.



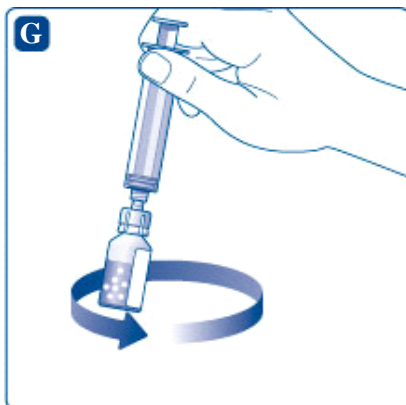
Hold the syringe with the solvent vial upside down. Pull the plunger to draw the solvent into the syringe.



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.

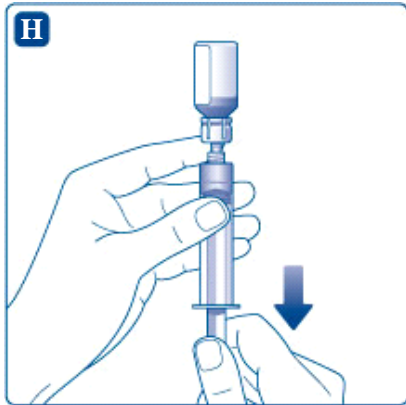
If a larger dose is needed, repeat the procedure in a separate syringe until the required dose is reached.

Important information

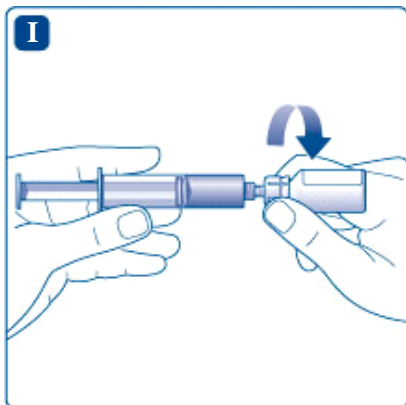
Once prepared, NovoThirteen for injection should be used immediately.

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’.

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 in the vein. Follow the injection procedure as instructed by your doctor.



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.

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

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 sodium chloride 0.9%, solution for injection (see section 3 'How to use NovoThirteen - Use in small children').

User instruction 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 6.0 ml sodium chloride 0.9%, solution for injection, into the 10 ml syringe. Slowly inject the 6.0 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.

In case of any questions ask your doctor or nurse.