PRODUCT MONOGRAPH

Schedule D

Tretten®

Catridecacog

Recombinant Coagulation Factor XIII A-Subunit

Lyophilized Powder

2500 IU per vial (15 mg/vial)

Professed

Coagulation Factor

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TRETTEN®

catridecacog

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	White lyophilized powder to be reconstituted with solvent for injection 2500 IU per vial (15 mg/vial)	Sodium chloride, sucrose
For a complete listing of nonmedicinal ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING section.		

DESCRIPTION

Tretten® (catridecacog) is a recombinant, human FXIII-A_2 homodimer composed of two FXIII A-subunits. It is structurally identical to human FXIII A-subunit [A_2]. The FXIII A-subunit is a 731 amino acid chain with an acetylated N-terminal serine. When FXIII is activated by thrombin, a 37 amino acid peptide is cleaved from the N-terminus of the A-subunit. **Tretten®** is manufactured as a soluble protein in yeast (*Saccharomyces cerevisiae*) production strain containing the episomal expression vector, pD16. It is subsequently isolated by homogenization of cells and purification by several chromatography steps. No animal derived or human proteins are used in the manufacturing process.

INDICATIONS AND CLINICAL USE

Tretten® (catridecacog) is indicated for routine prophylaxis for bleeding in adult and pediatric patients with congenital Factor XIII A-subunit deficiency.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Tretten® (catridecacog) should not be used for prophylactic treatment of bleeding in patients with congenital factor XIII B-subunit deficiency.

FXIII B-subunit deficiency is associated with a much reduced half-life of the administered pharmacologically active A-subunit. The subunit deficiency of patients should be known prior to treatment.

Considering that the posology and the FXIII concentration in **Tretten®** may be 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.

Patients should be advised to store the product according to the described storage conditions (see STORAGE AND STABILITY). 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 rFXIII. Increased levels of non-proteolytically activated rFXIII may increase the risk of thrombosis.

Hematologic

Thrombosis: In case of predisposition to conditions of thrombosis, caution should be exercised due to the fibrin-stabilizing effect of **Tretten®**. A stabilization of the thrombus might occur, resulting in increased risk of vessel occlusions.

Immune

Hypersensitivity Reactions: As **Tretten®** is a protein it may cause allergic reactions including anaphylactic reaction. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis.

If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately and future treatment with **Tretten®** should not be given.

Antibody Formation: Inhibitor formation to **Tretten®** therapy has not been detected in clinical trials. Inhibitors may be suspected in the event of lack of therapeutic response observed as clinical bleeding or demonstrated by laboratory findings including FXIII activities that fail to reach expected levels. In the event that inhibitors are suspected, analysis for antibodies should be performed.

Special Populations

Pregnant Women: There is no clinical data from the use of **Tretten®** in pregnant women. Animal studies are insufficient with respect to reproductive toxicity as **Tretten®** has not been studied in pregnant animals. The potential risk to humans is not known. **Tretten®** should be avoided during pregnancy unless the benefits clearly outweigh the risks.

Labour and Delivery: Tretten® has not been studied for use during labour and delivery.

Nursing Women: It is unknown whether **Tretten®** is excreted in human breast milk. The excretion of **Tretten®** in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with **Tretten®** should be made taking into account the benefit of breast-feeding to the child and the benefit of **Tretten®** therapy to the mother.

Fertility: No effects on reproductive organs are seen in non-clinical studies.

Pediatrics: Analyses of data from pediatric patients included in clinical trials have not identified differences in treatment response according to age. Data from six children less than 6 years of age was obtained from a pharmacokinetics study.

Geriatrics: Clinical studies of **Tretten®** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Hepatic Impairment: Patients with hepatic impairment have not been studied. **Tretten®** may not be effective in patients with hepatic impairment and decreased levels of FXIII B-subunits.

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

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials, **Tretten®** has been administered to 82 patients with congenital factor XIII A-subunit deficiency (3112 doses). 21 patients were between 6 and 18 years of age. Of the 82 patients, 67 patients were exposed to **Tretten®** in the phase 3 trials (F13CD-1725 and F13CD-3720), 9 patients were exposed in the Phase 1 trial (F13-1663), and 6 patients aged less than 6 years old were exposed to **Tretten®** in the pediatric trial (F13CD-3760) and the extension to the pediatric trial (F13CD-3835). There have been a total of 986 exposures to **Tretten®** in pediatric subjects. These clinical trials were all open label trials.

The most frequent adverse drug reactions are non-neutralizing antibodies. Non-neutralizing antibodies have been seen in 4 of the 82 exposed patients with congenital FXIII deficiency. The four events of non-neutralizing 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 **Tretten®**. All 4 patients received at least 2 doses of **Tretten®**. The antibodies had no inhibitory effect and the patients did not experience any adverse events or bleeding in association with these antibodies. All patients had no increase in antibody levels following repeated dosing with **Tretten®** or other FXIII containing products and the antibodies were transient in all patients.

Tretten® has also been administered to 122 healthy volunteers in four completed clinical trials (234 doses). In a study including 50 healthy male subjects, one subject developed low-titer, transient non-neutralizing antibodies after receiving the first dose of **Tretten®**. 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-neutralizing antibodies were found to be of no clinical significance.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following table summarizes the adverse drug reactions at a frequency of ≥ 1% in the pivotal trial F13CD-1725 and the phase 3 extension trial F13CD-3720.

Table 1 - Summary of Treatment Emergent Adverse Events with Possible or Probable Relation to Tretten® at a Frequency of ≥ 1% in the Pivotal Trial F13CD-1725 and the Phase 3 Extension Trial F13CD-3720

	F13CD-1725 F13CD-3720 35 IU/kg		
	N	**%**	**E**
Number of Subjects	67		
All Adverse Events	19	28.4	20
Blood And Lymphatic System Disorders	**3**	**4.5**	**3**
Leukopenia	2	3.0	2
Neutropenia	1	1.5	1
General Disorders And Administration Site Conditions	**1**	**1.5**	**1**
Injection site pain	1	1.5	1
Injury, Poisoning And Procedural Complications	**5**	**7.5**	**6**
Incorrect dose administered	3	4.5	4
Limb injury	1	1.5	1
Overdose	1	1.5	1
Investigations	**7**	**10.5**	**7**
Antibody test positive (non-neutralizing)	4	6.0	4
Fibrin D dimer increased	1	1.5	1
Alanine aminotransferase increased	1	1.5	1
Blood alkaline phosphatase increased	1	1.5	1
Musculoskeletal And Connective Tissue Disorders	**2**	**3.0**	**2**
Pain in extremity	1	1.5	1
Arthralgia	1	1.5	1
Nervous System Disorders	**1**	**1.5**	**1**
Headache	1	1.5	1

N: Number of subjects with adverse event
%: Proportion of subjects with adverse event
E: Number of adverse events

In the pivotal trial F13CD-1725, a total of 13 adverse events were evaluated by the investigator to be possibly or probably related to trial product. All events except one positive antibody test were classified as mild events, and all events were characterised by full recovery. 34 patients from the F13CD-1725 trial continued into the F13CD-3720 extension trial and 26 new patients were enrolled into the extension trial. A total of 7 adverse events in F13CD-3720 were evaluated by the investigator to be possibly or probably related to trial product.

One patient with a pre-existing neutropenia experienced a mild aggravation of neutropenia and leukopenia during treatment with **Tretten®**. Following discontinuation of **Tretten®** the patient's neutrophil count returned to levels similar to those prior to treatment with **Tretten®**.

In the pediatric trial (F13CD-3760) six children less than 6 years old were exposed to one single i.v. dose of **Tretten®** 35 IU/kg. The single i.v. injection was well tolerated and no thromboembolic adverse events were reported. Furthermore, no treatment emergent adverse events with possible or probable relation to **Tretten®** were reported. Results of safety laboratory parameters and other safety-related examinations did not indicate clinically relevant changes as a result of the rFXIII administration. No anti-rFXIII antibodies were detected in any of the patients.

In the pediatric extension trial (F13CD-3835) six subjects between the ages of 1 and 6-years-old were exposed to **Tretten®** for a total of 214 doses over 16.6 subject years. Subjects received 35 IU/kg **Tretten®** every 28 days for 1.8 to 3.5 years. Two non-serious adverse events (lymphopenia and gastroenteritis) in 2 subjects were assessed as probably or possibly related to **Tretten®** by the investigator. No thromboembolic adverse events or anti-rFXIII antibodies were reported.

Abnormal Hematologic and Clinical Chemistry Findings

No clinically relevant trends in the investigated parameters of coagulation, hematology, biochemistry and urinalysis were observed following **Tretten®** administration. No sign of systemic activation of the coagulation cascade was observed.

Post-Market Adverse Drug Reactions

In a post-authorization safety study transient non-neutralizing antibodies were seen in a child with congenital FXIII deficiency after several years of treatment with **Tretten®**. No clinical findings were associated with these antibodies.

DRUG INTERACTIONS

Drug-Drug Interactions

Coagulation Factor Concentrates
There is no clinical data available on interaction between **Tretten®** (catridecacog) and other medicinal products.

A potential synergistic effect of combined treatment with **Tretten®** (17 times the recommended human dose) and rFVIIa (11 times the recommended human dose) in an advanced cardiovascular model in cynomolgus monkey was seen resulting in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **Tretten®** (catridecacog) is intended for intravenous administration only.
- **Tretten®** treatment should be initiated under the supervision of a physician experienced in the treatment of rare bleeding disorders. The congenital Factor XIII A-subunit deficiency should be confirmed by appropriate diagnostic procedures.
- The on-demand treatment of acute bleeds or breakthrough bleeds with **Tretten®** has not been studied in clinical trials. An alternative treatment should be considered in such situations.
- Although expressed in the same unitage (IU), the posology of **Tretten®** is different from the dosing schedule of the other FXIII containing products.
- Patients should be advised to store the product according to the specified storage conditions (see STORAGE AND STABILITY). Following reconstitution, the product should be used immediately.

Recommended Dose and Dosage Adjustment

The recommended dose is 35 IU/kg body weight approximately once monthly, administered as an intravenous bolus injection.

The dose volume in mL to be administered to patients weighing at least 24 kg can be calculated using the formula below:

Dose volume in mL = 0.042 x Body weight in kilograms

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.

Pediatric Population

No dose adjustment is required when **Tretten®** is used in pediatric patients, and the dose of 35 IU/kg body weight should be used.

When **Tretten®** is administered to small children a further dilution of the product might be necessary. If the body weight of the child is less than 24 kg, the reconstituted **Tretten®** should be diluted with 6.0 mL of 0.9% sodium chloride solution for injection. Once diluted with 6.0 mL of 0.9% sodium chloride solution for injection, the dose volume for the reconstituted **Tretten®** can be calculated using the formula below:

Dose volume in mL of diluted product = 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.

Reconstitution

Tretten® Vial Size	Volume of Solvent to be Added to Vial	Approximate Concentration After Reconstitution
2500 IU/vial (15 mg/vial)	3 mL	833 IU/mL (5 mg/mL)

After reconstitution with the sterile water for injection, the concentration of the solution in the vial is approximately 833 IU/mL (5 mg/mL) catridecacog.

If the reconstituted **Tretten®** is diluted with 0.9% sodium chloride solution for injection, as described above for patients weighing less than 24 kg, the concentration of the solution is 299 IU/mL (1.8 mg/mL) catridecacog.

For detailed instructions on how to reconstitute and administer Tretten® refer to PART III of the Product Monograph.

Administration

- Following reconstitution the product should be administered separately and not mixed with infusion solutions nor be given in a drip.
- The reconstituted product is a clear colourless solution. Reconstituted **Tretten®** should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.
- Administer **Tretten®** as a slow bolus intravenous injection at a rate not exceeding 1-2 mL/minute.
- Any unused **Tretten®** should be discarded. Do not freeze reconstituted **Tretten®** or store it in syringes (see STORAGE AND STABILITY).

Monitoring

If during monitoring FXIII activity fails to reach expected levels or if reduced therapeutic effect is observed, analysis for inhibitors should be performed [see WARNINGS AND PRECAUTIONS: Immune, Antibody Formation].

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the reported cases of **Tretten®** overdosing, no clinical symptoms have been observed.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

In plasma, FXIII circulates as a heterotetramer [A_2B_2] composed of two FXIII A-subunits and two FXIII B-subunits held together by strong non-covalent interactions. The FXIII B-subunit acts as carrier molecule for the FXIII A-subunit in circulation, and is present in excess in plasma. When FXIII A-subunit is bound to FXIII B-subunit 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 carrier 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 enhance platelet and clot adhesion to injured tissue.

Tretten® is a protransglutaminase (rFXIII [rA_2] homodimer) and it is structurally identical to the human FXIII A-subunit [A_2]. **Tretten®** (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]. **Tretten®** has been shown to be activated by thrombin in the presence of Ca^{2+}. Activated **Tretten®** has been shown to increase mechanical strength of fibrin clots and retard fibrinolysis in a dose-dependent manner. **Tretten®** has been shown to enhance platelet adhesion to the site of injury. Thus, **Tretten®** has been shown to have the same pharmacodynamic properties in plasma as endogenous FXIII.

Pharmacodynamics

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.

Pharmacokinetics

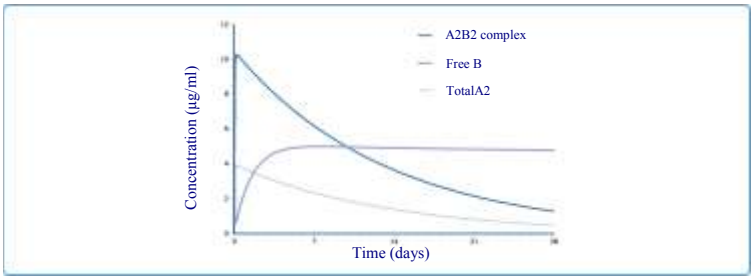

Figure 1 - Simulated example of Total A_2, A_2B_2 complex and Free B in plasma as determined by ELISA following single intravenous administration of 35 IU/kg to patients with congenital FXIII deficiency

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

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

When rFXIII [rA_2] is administered to patients with FXIII A-subunit deficiency or to healthy subjects, rA_2 forms a heterotetramer complex [rA_2B_2] with free B-subunit resulting in a rapid decrease of the plasma concentration of free B-subunit after rFXIII administration. In parallel to this, a rapid increase is observed for the concentration of the heterotetramer [rA_2B_2, A_2B_2]. Following administration of 20, 50 or 75 U/kg (corresponding to 24, 60 and 89 IU/kg, respectively) of rFXIII to patients, the plasma concentrations of free B-subunit were essentially restored to pre-dose levels within 72 hours.

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

After a single dose of 35 IU/kg of rFXIII in healthy male subjects, the following geometrical mean values and coefficients-of-variation (CV%) across subjects were calculated to provide estimates for a number of pharmacokinetic (PK) parameters for Novo Nordisk rFXIII, based on FXIII activity profiles measured by the Berichom® assay. Prior to calculation of PK parameters, the FXIII activity profiles were adjusted for the endogenous FXIII plasma activity at baseline for the individual subjects.

Clearance was estimated to be 0.13 mL/h/kg (CV=36.5%), the half-life estimate was 11.1 days (CV=64.5%) and volume of distribution at steady state had an estimate of 47.1 mL/kg (CV=24.7%).

The initial baseline-adjusted geometrical mean activity at 30 minutes post-dosing was 0.85 IU/mL (CV=24.2%) which decreased to 0.11 IU/mL (CV=85.5%) 28 days post-dose. The mean $AUC_{0\text{-}28days}$ was 220.3. IU*h/mL (CV=23.8%) and the mean $AUC_{infinity}$ was 277.6 IU*h/mL (CV=47.2%).

Pediatric population

In a pharmacokinetic trial six children (age 1 to less than 6 years old) with congenital FXIII A-subunit deficiency were exposed to one single i.v. dose of **Tretten®** 35 IU/kg. The geometric mean $t_{½}$ of FXIII was 15 days (range: 10 to 25 days). In this trial, the mean clearance in children was 0.15 mL/h/kg.

STORAGE AND STABILITY

Store in refrigerator (2°C - 8°C). Store in the original package in order to protect from light. Do not freeze to prevent damage to the solvent vial.

From a microbiological point of view and to avoid formation of non-proteolytically activated **Tretten®**, the product should be used immediately after reconstitution. Increased levels of non-proteolytically activated **Tretten®** may increase the risk of thrombosis.

If the reconstituted product is not used immediately, it should be used within 3 hours of reconstitution, and can be stored at room temperature during this period. Any unused product stored at room temperature for 3 or more hours should be discarded.

If the reconstituted product is not administered immediately, it should be stored in the refrigerator at 2°C - 8°C for no longer than 24 hours. After this period the product should be discarded.

If the product is diluted with 0.9% sodium chloride solution for injection (for those patients weighing less than 24 kg), the storage and stability recommendations specified above are still applicable.

Do not freeze reconstituted **Tretten®** or store it in syringes.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each pack contains:

- 1 vial with white powder for solution for injection containing 2500 IU (15 mg) catridecacog
- 1 vial with solvent (sterile water for injection) for reconstitution containing 3.2 mL
- 1 sterile vial adapter for reconstitution

Powder for Reconstitution
Tretten® (catridecacog) is supplied as a white, lyophilized powder in single-use vials. The vials are made of Type I glass, closed with a latex-free chlorobutyl rubber stopper and sealed with an aluminum cap. The vials are equipped with a tamper-evident snap-off plastic cap.

The following non-medicinal ingredients are found in **Tretten®**: L-histidine, polysorbate 20, sodium chloride, and sucrose.

Solvent
The solvent for reconstitution of **Tretten®** is sterile water for injection and is supplied as a clear colorless solution. The vials are made of Type I glass closed with a latex-free bromobutyl rubber disc, and covered with aluminum cap. The closed vials are equipped with a tamper-evident snap-off plastic cap.

Content of 3 mL Reconstituted **Tretten®**

Content	**Per Vial***
Catridecacog	2500 IU (15 mg)
L-histidine	9.30 mg
Polysorbate 20	0.30 mg
Sodium chloride	8.70 mg
Sucrose	174.0 mg

*Values are given per 3 mL reconstituted Tretten®

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Catridecacog

Chemical name: Recombinant Coagulation Factor XIII A-Subunit (rFXIII A-Subunit)

Molecular formula: $C_{3708}H_{5735}N_{1013}O_{1111}S_{28}$ (acetylated N-terminal Serine)

Molecular mass: 83.2 kDa

Structural formula: The structural formula of the rFXIII A-subunit is provided below:

SETSRTAFGGRRAVPPNNSNAAEDDLPTVELQGVVPRGVNLQEFLNVTSVHLFKERWDTN
KVDHHTDKYENNKLIVRRGQSFYVQIDFSRPYDPRRDLFRVEYVIGRYPQENKGTYIPVPI
VSELQSGKWGAKIVMREDRSVRLSIQSSPKCIVGKFRMYVAVWTPYGVLRTSRNPETDTY
ILFNPWCEDDAVYLDNEKEREEYVLNDIGVIFYGEVNDIKTRSWSYGQFEDGILDTCLYV
MDRAQMDLSGRGNPIKVSRVGSAMVNAKDDEGVLVGSWDNIYAYGVPPSAWTGSVDIL
LEYRSSENPVRYGQCWVFAGVFNTFLRCLGIPARIVTNYFSAHDNDANLQMDIFLEEDGN
VNSKLTKDSVWNYHCWNEAWMTRPDLPVGFGGWQAVDSTPQENSDGMYRCGPASVQA
IKHGHVCFQFDAPFVFAEVNSDLIYITAKKDGTHVVENVDATHIGKLIVTKQIGGDGMMDI
TDTYKFQEGQEEERLALETALMYGAKKPLNTEGVMKSRSNVDMDFEVENAVLGKDFKLS
ITFRNNSHNRYTITAYLSANITFYTGVPKAEFKKETFDVTLEPLSFKKEAVLIQAGEYMGQL
LEQASLHFFVTARINETRDVLAKQKSTVLTIPEIIIKVRGTQVVGSDMTVTVEFTNPLKETL
RNVWVHLDGPGVTRPMKKMFREIRPNSTVQWEEVCRPWVSGHRKLIASMSSDSLRHVYG
ELDVQIQRRPSM (731)

Physicochemical properties:

Description	White powder for solution for injection. The reconstituted preparation is a clear, colourless solution. The reconstituted solution has a pH of approximately 8.0.
Aqueous pH-solubility profile	Above pH 7, full solubility is seen in aqueous solutions. Between pH 3 and 7 a significant decrease in solubility is seen, reaching the lowest level near pH 5. Below pH 3 the protein is totally unfolded.
pK_a, pI value	The pI value is 5.9 determined by isoelectric focusing in a polyacrylamide gel.

Product Characteristics

Catridecacog is produced in *Saccharomyces cerevisiae* as the N-acetylated mature protein with no post-translational modifications. Furthermore, no disulfide linkages are present. The higher order structure of catridecacog is provided in the figure below showing the secondary and tertiary structures and the active site of each monomer. The N-terminal activation peptide, consisting of amino acids 1-37 which is cleaved off during activation by thrombin, is drawn as a bold line.

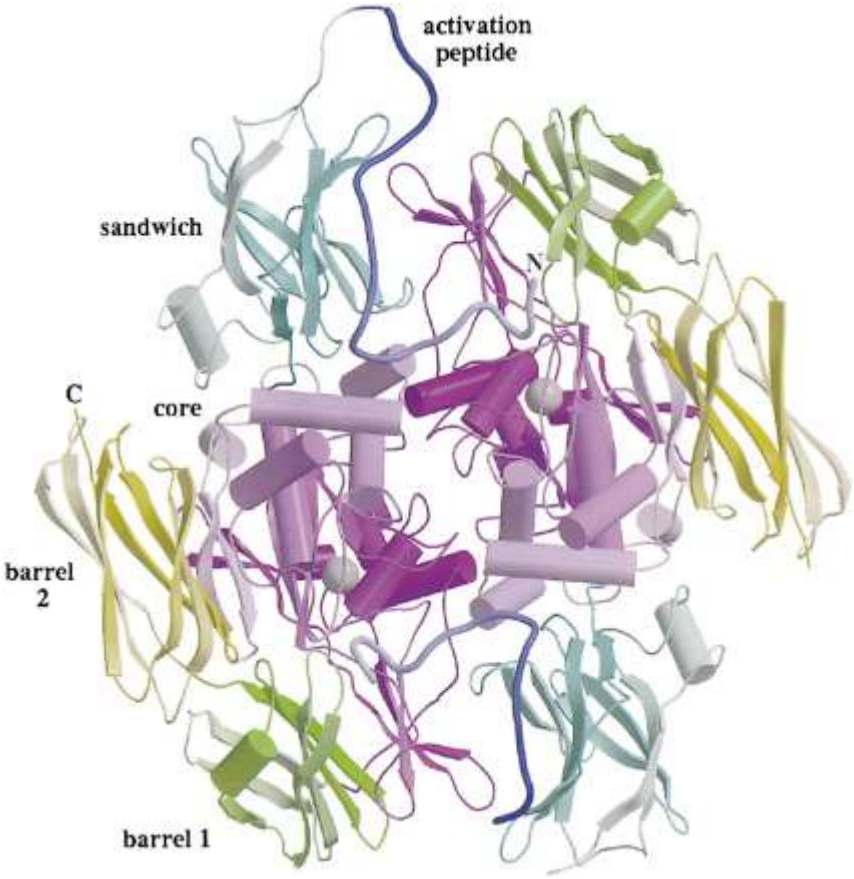

Figure 2: Higher order structure of rFXIII (A_2 homodimer)
Cylinder: alpha helix; Arrow: beta strand; Gray sphere: active site. N- and C-termini and structural domains of one A-subunit are labelled

CLINICAL TRIALS

Study Demographics and Trial Design

Table 2 - Summary of Patient Demographics for Pivotal Clinical Trial in Congenital FXIII Deficiency

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
F13CD-1725	Multi-centre, multi-national, open-label, single-arm, multiple dosing phase 3 trial evaluating the efficacy and safety of monthly replacement therapy with rFXIII in prevention of bleeding episodes associated with congenital FXIII deficiency	52-week treatment period of monthly (28±2 days) doses of 35 IU/kg rFXIII. Intravenous injection	41	Mean = 26.4 years Range = 7.0 – 60.0 years	18 Females 23 Males

The demographics of the trial population at baseline are presented in Table 2. The mean age was 26.4 years, and the gender distribution was approximately equal. The majority (68%) of patients were Caucasian. The age range of the trial population was 7 – 60 years.

Table 3 - Summary of Patient Demographics for Pediatric Clinical Trial in Congenital FXIII Deficiency

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
F13CD-3760	Multi-centre, multi-national, open-label, single dose trial, evaluating PK and safety of one i.v. dose of rFXIII in children (1 to less than 6 years old) with congenital FXIII A-subunit deficiency	Single dose of 35 IU/kg rFXIII. Intravenous injection	6	Mean = 2.7 years Range = 1 – 4 years	3 Females 3 Males

The demographics of the trial population at baseline are presented in Table 3. The mean age was 2.7 years, and the gender distribution was equal. Three children were Asian, two children were Caucasian and one child was African American. The age range of the trial population was 1 – 4 years.

Study Results
A single pivotal trial (F13CD-1725) was conducted to establish the efficacy and safety of monthly doses of 35 IU/kg in prevention of bleeding in patients with congenital FXIII A-subunit deficiency. 41 patients were dosed in the trial during a period of 52 weeks.

The primary endpoint for the pivotal trial was the rate of bleeding episodes requiring treatment with a FXIII-containing product. During the treatment period with **Tretten®** (434 patient months), 5 treatment-requiring bleeds were observed, corresponding to a mean rate of (5/434)*12 = 0.138 treatment-requiring bleeds per patient year (95% CI: [0.058; 0.332]).

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

Six children (less than 6 years old from a pharmacokinetics study) and 21 children between the age of 6 to less than 18 years old have been treated with **Tretten®** for a total of 986 exposures.

The suggested dose of 35 IU/kg has shown to be appropriate to provide hemostatic coverage in children with congenital FXIII A-subunit deficiency. **Tretten®** was well tolerated in this population.

DETAILED PHARMACOLOGY

Pharmacokinetics in Healthy Subjects

Pharmacokinetic parameters for healthy subjects are presented in Table 4. The primary evaluation is based on the geometric mean estimates from the NN1841-3788 trial, in which 50 subjects were exposed to a total of 98 doses of **Tretten®** at the intended dose level of 35 IU/kg rFXIII (two subjects were withdrawn following the initial dose). The estimated terminal half-life was 266 hours, which is equivalent to approximately 11 days. The mean volume of distribution at steady state (V_{ss}) was 47 mL/kg, mean residence time (MRT) was 15.5 days and mean clearance (CL) was 0.13 mL/h/kg.

Comparison of arithmetic mean estimates showed no major differences in pharmacokinetics across trials, with the dose-independent parameters (V_{ss}, $t_{½}$, MRT and CL) displaying relatively good agreement (Table 4). Some variation in estimates were observed across trials, which is to be expected given the degree of inter-subject variation in pharmacokinetics and the relatively few number of subjects for whom estimates are based.

Table 4 Pharmacokinetic Parameters – Healthy Subjects

	Trial ID	Dose **(IU/kg)**	N[a] **M; F**	$AUC_{0-\infty}$ **(h*IU/mL) mean (SD)**	C_{max} **(IU/mL) mean (SD)**	V_{ss} **(mL/kg) mean (SD)**	CL **(mL/h/kg) mean (SD)**	$t_{½}$ **(h) mean (SD)**	MRT **(h) mean (SD)**
Single dose	NN1841-3788	35	50M	*278 (47)*[b] 301 (142)	*0.85 (24)*[b] 0.87 (0.21)[c]	*47 (25)*[b] 48 (12)	*0.13 (37)*[b] 0.14 (0.05)	*266 (64)*[b] 303 (195)	*372 (67)*[b] 423 (282)
	F13-1661	30	4M; 4F[d]	207 (61)	0.80 (0.14)	45 (18)	0.15 (0.05)	219 (80)	313 (139)
	F13-1661	60	5M; 3F[e]	342 (204)	1.02 (0.14)	69 (18)	0.24 (0.16)	273 (161)	402 (232)
	NN1810-3733	12	8M	*97 (45)*[b]	*0.28 (17)*[b]	*52 (29)*[b]	*0.12 (46)*[b]	*270 (60)*[b]	*429 (52)*[b]
		35	8M	*177 (30)*[b]	*0.77 (13)*[b]	*58 (21)*[b]	*0.20 (37)*[b]	*176 (37)*[b]	*291 (31)*[b]
Multiple dose	F13-1662	12	6M; 2F	AUC_{0-24h} 16.9 (2.1)	0.87 (0.19)	-	-	346 (215)	-
	F13-1662	30	2M; 6F	AUC_{0-24h} 37.4 (5.5)	1.80 (0.25)	-	-	167 (50)	-

[a] N = number of subjects exposed. M = male; F = female.
[b] Geometric mean (CV) in *italics* (NN1841-3788 and NN1810-3733).
[c] C_{30min} (NN1841-3788).
[d+e] Of these, 4[d] and 7[e] subjects contributed to the PK assessment (F13-1661).

Pharmacokinetics in Patients with Congenital FXIII Deficiency
In the F13CD-1725 phase 3 trial of monthly administration of **Tretten®**, blood sampling for pharmacokinetics was performed immediately before and one hour after each monthly dose as well as 14 days after the initial dose of **Tretten®**. Based on FXIII activity as measured by the Berichrom® assay during the study period, the crude estimate of the half-life of **Tretten®** in these patients with congenital FXIII deficiency is 11.5 days. This is in agreement with the elimination pharmacokinetics estimated for healthy subjects.

The shape of the mean profiles for A_2B_2 tetramer and total FXIII A_2 corresponded to the FXIII activity profile, reflecting that concentrations increased sharply after each **Tretten®** administration followed by a gradual decline during the subsequent month.

Results on pharmacokinetics following single i.v. doses of 24, 60 or 89 IU/kg **Tretten®** to patients with congenital FXIII deficiency are available from the F13-1663 phase 1 trial. The terminal half-life ranged from 6 to 12 days. However, the results should be interpreted with caution as the pharmacokinetic evaluation was based on a total of 6 exposures in 6 subjects.

The pharmacokinetics in 6 pediatric patients less than 6 years old were investigated in study F13CD-3760. Age-stratified pharmacokinetic data from F13CD-3760 and from F13CD-1725 are presented in Table 5.

Table 5 Steady State Pharmacokinetic Parameters for Different Age Groups in Trials F13CD-3760 and F13CD-1725

Geometric Mean (CV %)	Study F13CD-3760	Study F13CD-1725†		
	1–5 years	6–11 years	12–17 years	18+ years
Patients, *n*	6	9	6	26
AUC_{0-28}, IU·h/mL*	248.6 (13)	251.7 (26)	217.1 (19)	245.2 (22)
C_{max}, IU/mL	0.67 (21)	0.75 (43)	0.67 (15)	0.76 (21)
C_{trough}, IU/mL	0.20 (22)	0.20 (25)	0.17 (28)	0.18 (22)
$t_{½}$, days	15.0 (34)	12.4 (21)	11.9 (32)	11.6 (18)

The table presents geometrical means (CV %).
*For F13CD-3760, AUC_{0-30} is presented.
†For F13CD-1725, PK calculations were based on a more sparsely sampled curve (three time points vs. six time points for F13CD-3760).
AUC, area under the concentration vs. time curve; C_{max}, maximal measured FXIII activity; CV, coefficient of variance; $T_{1/2}$, terminal half-life.

TOXICOLOGY

Carcinogenicity, Mutagenicity, Impairment of Fertility

Studies concerning carcinogenicity, mutagenicity and impairment of fertility in animals have not been performed.

Acute Toxicity

In the cynomolgus monkey, single doses of rFXIII were administered intravenously in doses ranging from 0-30 mg/kg rFXIII (~ 0- 5010 IU/kg, 0-143 fold the recommended clinical dose of 35 IU/kg). The dose-response relationship for rFXIII toxicity was shown to be steep. The animals either tolerated treatment with rFXIII or at higher doses (≥ 21.9 mg/kg ~≥ 3657 IU/kg, 104 fold the recommended clinical dose of 35 IU/kg) died or were sacrificed for humane reasons. Affected animals developed generalised occlusive coagulopathy (e.g. intravascular congestion, thrombosis and subsequent ischemic necrosis) in many organs and tissues consistent with a diagnosis of disseminated intravascular coagulation (DIC). Organs and tissues affected included adrenal glands, kidneys, eyes, lungs, heart, the gastrointestinal tract, pancreas, spleen, liver, brain, pituitary (neurohypophysis) and bone marrow thereby reflecting the systemic nature of the toxicity. The observed gross and microscopic changes correlated with the observed changes in clinical pathology parameters (hematology, coagulation and clinical chemistry). For further details please refer to Table 6.

Table 6: Overview of Single Dose Toxicity Studies

Study number	SBI 1220-175	SBI 1278-175	SBI 1249-175[1]
Species / strain	Cynomolgus monkey / *Macaca fascicularis*	Cynomolgus monkey / *Macaca fascicularis*	Cynomolgus monkey / *Macaca fascicularis*
Dose route	i.v.	i.v.	i.v.
Animals per dose/Sex	1 female	1 female	1 male (21.9 mg/kg), 1 male and 1 female (22.5 mg/kg)
Dose level (mg/kg)	0, 10, 17.5, 20 (Avecia DS)[3]	0, 20, 21.2, 22.5, 25, 30 (Avecia DS) [3]	21.9 and 22.5 (Avecia DS) [3]
Dose level (IU/kg)[2]	0, 1670, 2923 and 3340	0, 3340, 3540, 3758, 4175 and 5010	3657 and 3758
rFXIIIa^{o} in test article (%)[4]	0.19	0.33	0.26
Duration	1 day, 8 days observation	1 day, 8 days observation	1 day
GLP status[5]	Non-GLP	Non-GLP	GLP
Note worthy findings	None	Animals administered 22.5 and 30 mg/kg died or were sacrificed moribund Day 5 and 1, respectively. Histopathology revealed widespread thrombosis and ischemic necrosis consistent with the diagnosis of DIC	All monkeys died Day 1. Histopathology revealed widespread thrombosis and ischemic necrosis consistent with DIC.

[1]In this study both single and repeat doses were given, results from single doses is tabulated in this table and repeat doses in Table 7
[2]rFXIII was administered in mg/kg the content in IU is not known, the dose level in IU/kg is an approximate dose based on 1 mg= 167 IU
[3]Drug substance manufactured by Avecia
[4]rFXIIIa^{o} refers to non-proteolytically activated FXIII
[5]Good Laboratory Practice

Repeat Dose Toxicity

Repeat-dose toxicity studies were conducted for up to 4 weeks in rats and 27 weeks in cynomolgus monkeys.

Repeated doses of rFXIII were generally well tolerated up to 5-15 mg/kg/day in the rat (24-72 fold the recommended clinical dose of 35 IU/kg) and up to 3-8 mg/kg/2 weeks in the cynomolgus monkey (14 to 38 fold the recommended clinical dose of 35 IU/kg), for details including dose interval and noteworthy findings please refer to Table 7.

The toxicity seen (thrombosis, ischemic necrosis and death) after acute and repeated dosing in cynomolgus monkey is considered related to the cross-linking role of activated FXIII and formation of high molecular weight protein complexes (HMEX) causing blood vessel obstruction. Subsequent ischemia and cellular damage occurs and leads to activation of the

coagulation cascade, which in the worst case leads to fatal DIC. The histological picture, clinical pathology and the correlation to presence of HMEX in plasma support this proposed sequence of events. The toxicity seen is therefore considered to represent exaggerated pharmacology.

In monkeys dying or sacrificed for humane reason, clinical pathology demonstrated alterations in coagulation, hematology and serum chemistry corresponding to the finding of generalised occlusive coagulopathy (ischemic necrosis) in various organs.

Lymphoid hyperplasia was seen in the spleen in the 4 weeks rat study (NN209502) and one of the repeat dose toxicity studies in monkey (SBI 1266-175). This is a common immunological reaction when administrating a foreign protein to both rat and monkey. The finding is a reversible adaptive response to a species foreign protein but is not considered adverse.

There was not a direct correlation between lymphoid hyperplasia in the spleen and anti-FXIII-antibodies; however the lymphoid hyperplasia may also reflect antibody production towards yeast host-cell-proteins or product-related impurities.

Glomerulopathy/focal nephropathy was noted as a normal background finding in the rat and cynomolgus monkey, but in one monkey study report glomerulopathy was noted as possibly treatment-related. The conclusion was that there were no renal lesions associated with the rFXIII test article. The glomerulopathy reported as treatment-related in study SBI 1266-175 was considered to be similar to those seen in other monkeys, including controls in SBI 1394-175. Based on this, 12.5 mg/kg/2 weeks was considered to be the NOAEL (No Observed Adverse Effect Level) of the 4-weeks repeat dose toxicity study in monkey, rather than the 8 mg/kg/2 weeks concluded in study SBI 1266-175.

In conclusion, the toxicity seen in acute- and repeat-dose toxicity studies is well understood and is an expected pharmacological response to high dose levels rFXIII/rFXIIIa, consistent with the known cross-linking role of endogenous FXIII/rFXIIIa as described in the literature. Consistent with the species foreign nature of rFXIII an immunological response was seen both in rat and cynomolgus monkey. This was seen as lymphoid hyperplasia in the spleen and/or as development of anti-drug antibodies.

Table 7: Overview of Repeat Dose Toxicity Studies

Study #	**NN209517**	**NN209502**	**SBI 1249-175**	**SBI 1394-175**	**SBI 1266-175**	**NN205255**
Species	Rat	Rat	Monkey	Monkey	Monkey	Monkey
Dose route	i.v.	i.v.	i.v.	i.v.	i.v.	i.v.
Dose duration	< 1 week	4 weeks	< 1 week (2 repeat doses)	2 weeks	4 weeks	13 and 27 weeks
Dose interval	Daily	Daily	3 days (72 hours)	Daily	2 weeks	2 weeks
Dose levels (mg/kg)	0, 5 and 15 (NN DS) [2]	0, 1, 5, 15 (NN DS)[2] 1 and 5 (Avecia DS)[3]	0, 12.5 and 17.5 (Avecia DS) [3]	0, 0.3. 3 and 6 (Avecia DS) [3]	0, 5, 8 and 12.5 (Avecia DS) [3]	0, 1, 3 and 10 (Avecia DS) [3]
Dose levels (IU/kg)	0, 835 and 2505	0, 167, 835 and 2505	0, 2088, 2923[1]	0, 50, 501, 1002[1]	0, 835, 1336, 2088[1]	0, 167, 501, 1670[1]
rFXIIIa^{o} in test article (%)[4]	< 0.15	< 0.15 (NN DS) [2] 0.16 (Avecia DS) [3]	0.26	1.02	0.26	0.53
No of animals and sex per dose group	5 M and 5 F (main), 6 males and 6 females (TK)	10 M and 10 F (main), 5 M and 5 F (recovery), 3-6 M and 3-6 F (TK)	1-2 M and 0-1 F	3-5 M and 3-5 F	3-5 M and 3-5 F	3-15 M and 3-15 F
NOAEL (mg/kg)/[IU/kg][1]	15 [2505]	15 [2505] (NN DS) [2] 5 [835] (Avecia DS) [3]	No NOAEL	6 [1002]	8 [1336]	3 [501]

Study #	NN209517	NN209502	SBI 1249-175	SBI 1394-175	SBI 1266-175	NN205255
Note-worthy finding	None	Reversible lymphoid hyperplasia in the spleen was seen in males administered 15 mg/kg rFXIII (NN DS) [2] and in males and females administered 1 and 5 mg/kg rFXIII (Avecia DS).	All monkeys but one administered rFXIII died (or were sacrificed) after 2 repeat doses of rFXIII administered 72 hours apart (12.5 or 17.5 mg/kg). The cause of death was widespread thrombosis and ischemic necrosis consistent with DIC. One monkey survived administered 2 repeat doses of 12.5 mg/kg 72 hours apart.	None	Mild glomerulopathy in one out of six monkeys administered 12.5 mg/kg rFXIII. Reversible lymphoid hyperplasia in the spleen was seen in female monkeys administered 8 and 12.5 mg/kg.	One monkey out of 30 administered 10 mg/kg rFXIII died after a single dose. Cause of death thrombosis and ischemic necrosis.

[1] rFXIII was administered in mg/kg the content in IU is not known, the dose level in IU/kg is an approximate dose based on 1 mg= 167 IU
[2] Novo Nordisk manufactured drug substance
[3] Avecia manufactured drug substance
[4] rFXIIIa^{o} refers to non-proteolytically activated FXIII

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PART III: CONSUMER INFORMATION

Tretten®
catridecacog

This leaflet is part III of a three-part "Product Monograph" published when **Tretten®** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Tretten®**. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Tretten® is recombinant blood coagulation Factor XIII A-subunit. **Tretten®** is used to prevent bleeding in patients who do not have enough Factor XIII A-subunit.

What it does:
Tretten® replaces the missing Factor XIII A-subunit and helps to stabilize the initial blood clot.

When it should not be used:
Do not use **Tretten®** if you are allergic (hypersensitive) to catridecacog or to any ingredient in the formulation or component of the container.

Do not use **Tretten®** without talking to your doctor, if you are pregnant, planning to become pregnant, or are breast feeding.

What the medicinal ingredient is:
The medicinal ingredient is recombinant Factor XIII A-subunit (catridecacog).

What the non-medicinal ingredients are:
Tretten® contains the following non-medicinal ingredients: L-histidine, polysorbate 20, sodium chloride, and sucrose.

What dosage forms it comes in:
Tretten® comes as a freeze-dried powder containing 2500 IU/vial (corresponding to 15 mg/vial). The powder in the vial is reconstituted (dissolved) with the solvent (sterile water) that is supplied with your **Tretten®**. After reconstitution, 1 mL of solution contains 833 IU of catridecacog (corresponding to 5 mg/mL).

WARNINGS AND PRECAUTIONS

Once you have prepared **Tretten®** for injection it should be used immediately. For proper storage instructions see "Proper use of this medication" and "How to store it".

BEFORE you use **Tretten®** talk to your doctor if you have, or have ever had any of the following:

- A higher risk of blood clots forming (thrombosis), as **Tretten®** may increase the severity of a pre-existing clot.
- Liver damage.
- Experienced unexpected spontaneous bleeding during treatment with Factor XIII containing products. Antibodies against **Tretten®** could decrease the effectiveness of the treatment and thereby result in unexpected spontaneous bleeding episodes. **Contact your doctor immediately if bleeding occurs.**

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor if you are using or have recently used any other medicines, including medicines obtained without a prescription.

Do not use **Tretten®** and rFVIIa (another blood clotting factor) together.

PROPER USE OF THIS MEDICATION

Always use **Tretten®** exactly as your doctor has told you. You should check with your doctor if you are not sure.

Tretten® is given as an injection into a vein. For instructions on how to prepare and administer **Tretten®** please refer to the sections 'Preparing Your Injection' and 'Giving Your Injection' located at the end of this insert.

Once you have prepared **Tretten®** for injection it should be used immediately. This is because if not stored correctly, the medicine may no longer be sterile. Also, the amount of activated Factor XIII in the medicine may increase. Activated Factor XIII may increase the severity of a pre-existing blood clot. It is therefore important that you store **Tretten®** according to the storage instructions below.

Usual dose:
- Your dose will depend on how much you weigh.
- The usual dose is 35 IU for each kilogram of body weight.
- The injections are given once a month.

Overdose:
There is limited information on overdosing with **Tretten®**. None of the reported cases have had a medical consequence. If you have injected more **Tretten®** than you should, talk to your doctor immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget an injection of **Tretten®** talk to your doctor immediately. Do not take a double dose to make up for a forgotten dose.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor as soon as possible if you do not feel well while you are receiving treatment with **Tretten®**.

If you have an allergic reaction, see a doctor immediately. The signs may include:
- Hives
- Itching
- Swelling
- Difficulty breathing
- Low blood pressure (paleness and coldness of skin, rapid heartbeat)
- Feeling dizzy and sweating

*The following is not a complete list of side effects. For any unexpected effects while taking **Tretten®**, contact your doctor.*

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor**		**Stop taking drug and call your doctor immediately**
		Only if severe	**In all cases**	
Common	Headache	✓		
	Pain where injection is given	✓		
	Pain in legs and arms	✓		
	Your body may be more prone to infections	✓		
Not known	Hives			✓
	Itching			✓
	Swelling			✓
	Difficulty breathing			✓
	Paleness, coldness of skin, rapid heartbeat			✓
	Dizziness and sweating			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

- Keep out of the reach and sight of children
- Do not use **Tretten®** after the expiry date which is stated on the label and the outer carton
- Store in the original package in order to protect from light
- Store in a refrigerator
- Do not freeze

It is recommended to use the reconstituted product immediately.

If the reconstituted product is not used immediately, it should be used within 3 hours of reconstitution, and can be stored at room temperature during this period. Any unused product stored at room temperature for 3 or more hours should be discarded.

Alternatively, if the reconstituted product is not administered immediately, it should be stored in the refrigerator at 2°C - 8°C for no longer than 24 hours. After this period the product should be discarded.

If the product is diluted with 0.9% sodium chloride solution for injection (for those patients weighing less than 24 kg), the storage and stability recommendations specified above are still applicable.

Do not freeze reconstituted **Tretten®** or store it in syringes.

MORE INFORMATION

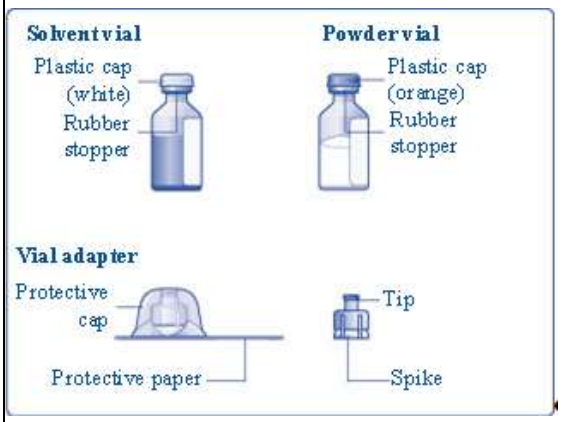
If you still have questions or would like more information, please contact your doctor.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novonordisk.ca or by contacting Novo Nordisk Canada Inc., at: 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

Last revised: June 2017

PREPARING YOUR INJECTION



To reconstitute and administer this product you will need the following tools: 10 mL syringe or size of syringe as most convenient according to injection volume, alcohol swabs, the vial adapter included, and an infusion set (tubing, butterfly needle).

Check the name and the colour of the package to make sure it contains the right product. Also check that the product has not passed the expired date.

Reconstitute only with the solvent provided with **Tretten®** (sterile water for injection).

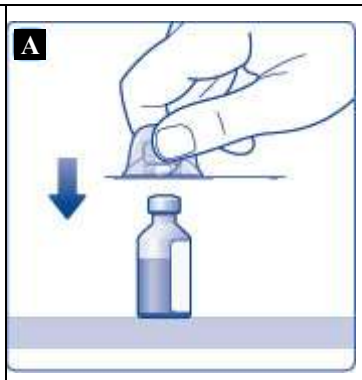
Always use sterile technique.

Before starting, wash your hands with soap and water and dry with a clean towel.

Bring the powder and solvent vials to room temperature, but not above 25°C. You can do this by holding the vials in your hands until they feel as warm as your hands.

Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry prior to use. Do not touch the rubber stoppers after wiping them.

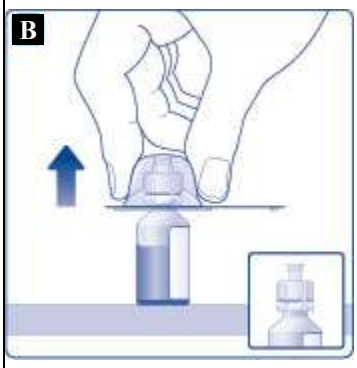
Step A



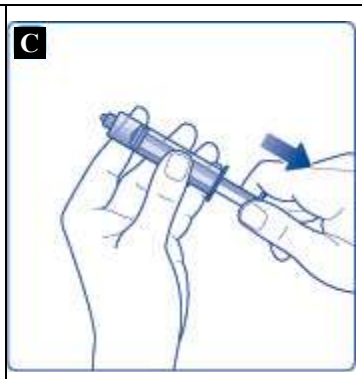
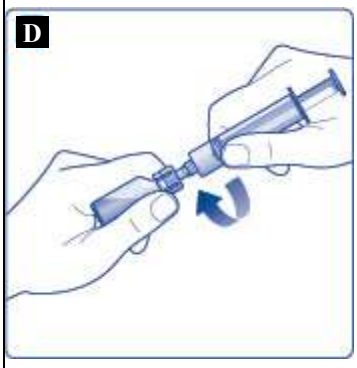
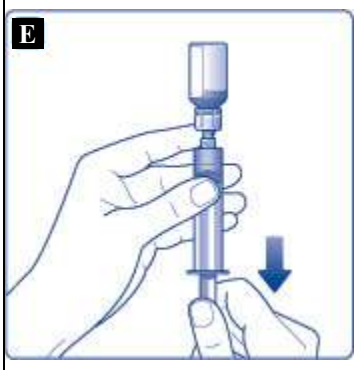
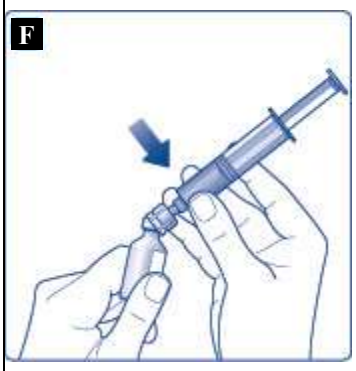
The product is reconstituted using the vial adapter included.

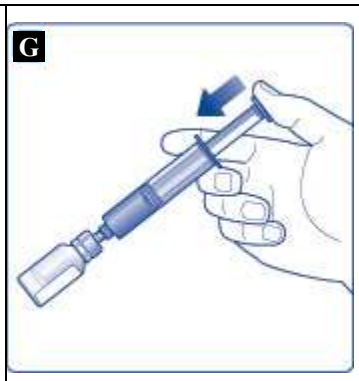
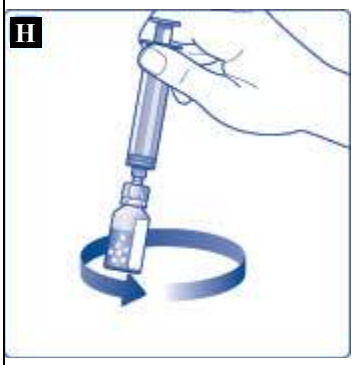
Remove the protective paper from the vial adapter, without taking the vial adapter out of the protective cap. If the protective paper is not fully sealed or if it is broken, do not use the vial adapter. Place the solvent vial on a flat and solid surface and attach the vial adapter to the solvent vial (sterile water for injection). Take care not to touch the spike on the vial adapter.

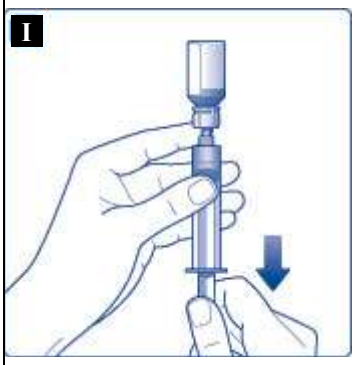
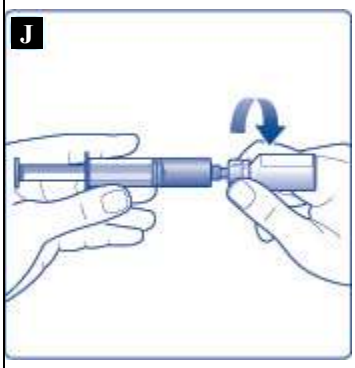
Step B



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

Step C		Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (3.2 mL sterile water).
Step D		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.
Step E		Hold the syringe with the solvent vial upside down. Pull the plunger to draw the solvent into the syringe.
Step F		Remove the empty solvent vial by tipping the syringe with the attached vial adapter.

Step G		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.
Step H		Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. Check the solution for bits and discolouration. If you notice either, do not use it. The reconstituted product is a clear, colourless solution. If you need a larger dose, repeat the procedure in a separate syringe until you have reached your required dose.
	Special Additional Instructions for Patients Weighing Less than 24 kg If the body weight is less than 24 kg, the reconstituted **Tretten®** should be diluted with 6.0 mL of 0.9% sodium chloride solution for injection. Your doctor will let you know if this is the case, and instruct you on how to dilute **Tretten®**. To dilute the reconstituted **Tretten®** the following tools are needed: a vial containing 0.9% sodium chloride solution for injection, a 10 mL syringe and alcohol swabs. <u>General Instructions for Dilution</u>: The dilution should be performed using sterile technique. Carefully draw exactly 6.0 mL of 0.9% sodium chloride solution for injection into the 10 mL syringe. Slowly inject the 6.0 mL of 0.9% sodium chloride solution for injection into the reconstituted **Tretten®** vial. Gently swirl the vial to mix the solution. The diluted solution is a clear, colourless solution. Check the injection solution for particles and for discolouration. If either is noticed, please discard. After dilution proceed to the step 'GIVING YOUR INJECTION'. **Important Information** Once you have prepared **Tretten®** it should be used immediately. This is because if left, the medicine may no longer be sterile. Also, the amount of activated **Tretten®** in the medicine will increase. Activated **Tretten®** may increase your risk of getting a blood clot (thrombosis). If the reconstituted product is not used immediately, it should be used within 3 hours of reconstitution, and can be stored at room temperature during this period. Any unused product stored at room temperature for 3 hours should be discarded. Alternatively, if the reconstituted product is not administered immediately, it should be stored in the refrigerator at 2°C - 8°C for no longer than 24 hours. After this period the product should be discarded.	

GIVING YOUR INJECTION		
Step I		Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw up the amount calculated for the injection.
Step J		Unscrew the vial adapter with the vial. The product is now ready for injection. Follow the injection procedure as instructed by your healthcare professional.
Step K		Safely dispose of the syringe, vial adapter, infusion set and vials. Any unused product or waste material should be disposed of in accordance with local requirements.