

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRETTEEN safely and effectively. See full prescribing information for TRETTEEN.

TRETTEEN, Coagulation Factor XIII A-Subunit (Recombinant)
For Intravenous Use. Lyophilized Powder for Solution for Injection
Initial U.S. Approval: [year]

INDICATIONS AND USAGE

TRETTEEN, Coagulation Factor XIII A-Subunit (Recombinant), is indicated for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.

TRETTEEN is not for use in patients with congenital factor XIII B-subunit deficiency.

DOSAGE AND ADMINISTRATION

For intravenous use only.

Dose:

- 35 international units per kilogram body weight once monthly to achieve a target trough level of FXIII activity at or above 10% using a validated assay. (2.1)
- Consider dose adjustment if adequate coverage is not achieved with a 35 IU/kg dose. (2.1)
- Once reconstituted, TRETTEEN may be diluted with 0.9% sodium chloride to facilitate measurement of small volumes. (2.2)

Rate: Do not exceed 1-2 mL per minute. (2.3)

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder in single-use vial containing 2000 - 3125 IU of recombinant coagulation factor XIII A-subunit.

- After reconstitution with 3.2 mL of sterile water for injection, each vial contains 667-1042 IU/mL of recombinant coagulation factor XIII A-subunit.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- Discontinue if allergic or hypersensitivity reactions occur. (5.1)
- Monitor patients for thrombosis. (5.2)
- Analyze for neutralizing antibodies if FXIII activity fails to reach expected levels or if reduced therapeutic effect is observed. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported in the clinical trials ($\geq 1\%$) were headache, pain in the extremities, injection site pain, D dimer increase. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-668-6777 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Do not administer TRETTEEN with recombinant factor VIIa.

USE IN SPECIFIC POPULATIONS

Pregnancy: No human or animal data available. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [m/year]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRETTEN, Coagulation Factor XIII A-Subunit (Recombinant), is indicated for routine prophylaxis for bleeding in patients with congenital factor XIII A-subunit deficiency.

TRETTEN is not for use in patients with congenital factor XIII B-subunit deficiency

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

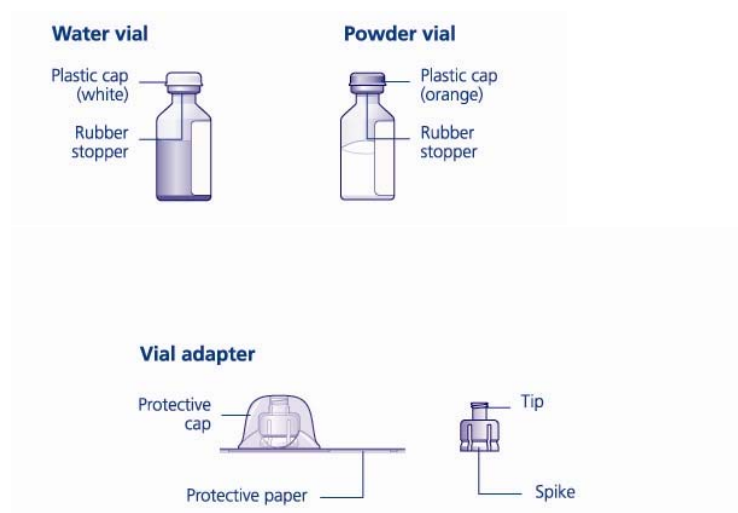
2.1 Dose

- Treatment should be initiated under the supervision of a physician experienced in the treatment of rare bleeding disorders.
- The dose for routine prophylaxis for bleeding in patients with congenital factor XIII (FXIII) A-subunit deficiency is 35 international units (IU) per kilogram body weight once monthly to achieve a target trough level of FXIII activity at or above 10% using a validated assay.
- Consider dose adjustment if adequate coverage is not achieved with the recommended 35 IU/kg dose.

A pharmacokinetic study was conducted in the FXIII congenitally deficient population evaluating five dose cohorts (2, 7, 24, 60 and 89 IU/kg) with blood sampling at 0.5, 1, 4, 8, 24, 48, 72 hours, and 7, 14, and 28 days. Samples were tested for FXIII activity by a chromogenic assay and for FXIII A₂B₂ tetramer levels by an ELISA, as well as for other analytes. It was found that FXIII tetramer levels were proportional to the observed FXIII activity up to the point of replacement of 100% of normal FXIII activity, but there was no increase in FXIII tetramer levels at higher levels of FXIII activity. A dose of 35 IU/kg is sufficient to replace 100% of FXIII activity in this population, and higher doses may not increase the levels of tetrameric Factor XIII.

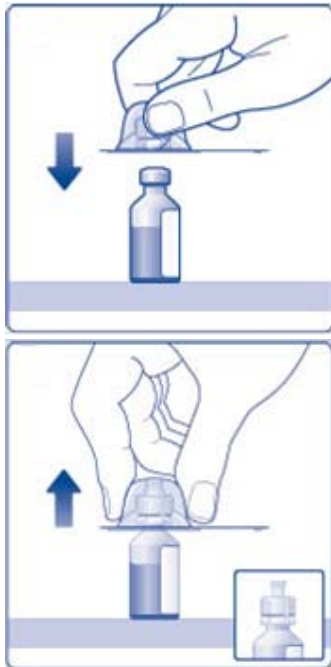
2.2 Reconstitution

Reconstitute only with sterile water for injection (provided with TRETTEN). The product can be reconstituted using the vial adapter included or a needle.



Reconstitute using the following procedures:

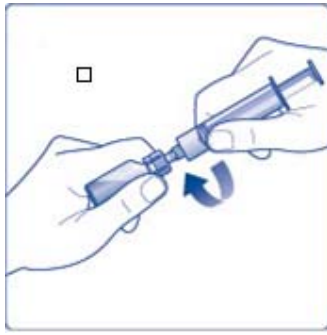
1. Use aseptic technique.
2. Wash hands before starting.
3. Bring TRETEN (white lyophilized powder) and sterile water for injection (diluent) to room temperature, but not above 25°C (77°F).
4. Remove the plastic caps from the two vials.
5. Clean the rubber stoppers on the vials with sterile alcohol swabs and allow them to dry before use.
6. Remove the protective paper from the vial adapter, but do not unscrew the protective cap. Attach the vial adapter to the diluent vial, without taking the vial adapter out of the protective cap. Once attached, remove the protective cap from the vial adapter by lightly squeezing the protective cap with your thumb and index finger as shown on the figure below.



7. Draw back the plunger of the sterile syringe and admit a volume of 3.2 mL air into the syringe.



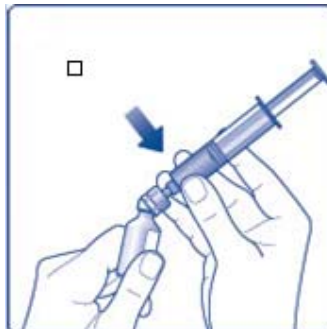
8. Screw the syringe onto the vial adapter on the diluent vial.



9. Inject the air from the syringe into the diluent vial until resistance is felt. Then hold the syringe with the diluent vial upside down and withdraw 3.2 mL water into the syringe.



10. Remove the empty diluent vial by tipping the syringe with the attached vial adapter.



11. Attach the syringe with the vial adapter to the powder vial. Hold the syringe slightly tilted with vial facing downwards. Push the plunger slowly to inject all water (3.2 mL) into the powder vial. **Do not inject the diluent directly on the TRETEN powder to avoid foaming.**



12. Gently swirl the vial until all material is dissolved. **Do not shake the vial.** The reconstituted TRETEN is a clear and colorless solution. Use the reconstituted TRETEN immediately. If not, store the solution refrigerated or at room temperature not to exceed 25°C (77°F) for up to three hours. Discard after three hours.



NOTE:

- For larger dose that requires multiple vials of TRETEN, reconstitute each additional vial using the same procedure with a separate syringe.
- For smaller dose that requires less than the full volume in the vial, reconstituted TRETEN may be diluted with 0.9% sodium chloride to facilitate measurement of small volumes. Discard remaining product.
- For home administration, any such changes should be communicated by the pharmacist or healthcare provider to the patient or family.

2.3 Administration

- Inspect the reconstituted TRETEN visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.
- Administer at a rate not exceeding 1-2 mL per minute.
- Do not administer with other infusion solutions.
- Do not administer as drip.

3 DOSAGE FORMS AND STRENGTHS

TRETEN, Coagulation Factor XIII A-Subunit (Recombinant), is available as a white lyophilized powder in single-use vial containing nominally 2500 IU per vial (2000 – 3125 IU) of recombinant coagulation factor XIII A-subunit. The actual amount of TRETEN in IU is stated on each carton and vial.

After reconstitution with the provided Sterile Water for Injection, each vial contains 667-1042 IU/mL recombinant coagulation factor XIII A-subunit.

4 CONTRAINDICATIONS

TRETEN is contraindicated in patients who have known hypersensitivity to the active substance or to any of the excipients [See Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

TRETTEN may cause allergic reactions. If signs or symptoms of anaphylaxis or hypersensitivity reactions (including urticaria, rash, tightness of the chest, wheezing, hypotension) occur, discontinue immediately and institute appropriate treatment.

5.2 Thromboembolic Risk

Thromboembolic complications may occur. Monitor patients with conditions that predispose to thrombosis for signs and symptoms of thrombosis after administration of TRETTEN.

5.3 Inhibitors

Inhibitory antibodies may occur with TRETTEN. Patients with inhibitory antibodies may manifest as an inadequate response to treatment. If expected plasma FXIII activity levels are not attained, or if breakthrough bleeding occurs while receiving prophylaxis, perform an assay that measures FXIII inhibitory antibody concentrations.

6 ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials ($\geq 1\%$), were headache, pain in the extremities, injection site pain, and increase in fibrin D dimer levels.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical development, TRETTEN was administered to 77 patients with congenital factor XIII A-subunit deficiency (3:2, male: female ratio) for a total of 1990 doses. Fifty patients (65%) were between the ages of 18 and 77 years (received 1338 doses), 21 patients (27%) were between the ages of 6 and less than 18 years old (received 560 doses), and 6 patients (8%) were less than 6 years old (received 92 doses). Patients were exposed for up to 4.5 years.

Of the 77 patients, 68 received 1979 monthly doses of 35 IU/kg of TRETTEN for routine prophylaxis of bleeding. Eleven single doses of TRETTEN have been administered to nine patients for pharmacokinetic investigations.

The adverse drug reactions reported included headache, pain in the extremities, pain at the injection site, and increase in fibrin D dimer levels (without evidence of thromboembolic events).

Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRETTEN with the incidence of antibodies to other products may be misleading.

Low level, non-neutralizing antibodies were seen in four of the 77 patients with congenital FXIII A-subunit deficiency. They were all under the age of 18 years. Three of these patients discontinued from trial after development of antibodies. All four patients received at least two doses, with at least one dose given subsequent to the formation of the non-neutralizing antibodies. These antibodies were not found to be of clinical significance.

In another study including 50 healthy subjects (29 males, 21 females), who were given 2 doses of TRETTEN, one subject developed low-titer, transient non-neutralizing antibodies after receiving the first dose of TRETTEN. The antibodies had no inhibitory activity, and the antibodies disappeared in the 6-month follow up.

7 DRUG INTERACTIONS

Thrombosis may occur if TRETEN is administered concomitantly with factor VIIa [See *Nonclinical Pharmacology (13.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with TRETEN. It is also not known whether TRETEN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRETEN should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether TRETEN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRETEN is administered to a nursing woman.

8.4 Pediatric Use

Pediatric patients in the phase 3 study and the extension study included 6 children in the age range 0-5, 12 children in the age range 6-12, and 9 adolescents in the age range 13-17 who were treated with TRETEN for a total of 652 exposures. Adverse reactions were more frequently reported in patients aged from 6 to less than 18 years old than in adults; a greater number of possible/probably trial drug related events were reported in the patients below 18 years of age (6 patients with 11 events in 27 enrolled patients) than in those above 18 years (3 patients with 3 events in 41 enrolled patients). Three patients under 18 years experienced non-neutralizing antibodies and were withdrawn from the study. A fourth pediatric patient who had a non-neutralizing antibody remained in the trial. No dose adjustment is required for pediatric age group.

8.5 Geriatric Use

The safety and efficacy of TRETEN in the geriatric population have not been established due to an insufficient number of patients.

10 OVERDOSAGE

One patient accidentally received a dose 2.3 times the recommended dose. No clinical signs and symptoms were observed.

11 DESCRIPTION

TRETEN, Coagulation Factor XIII A-Subunit (Recombinant), is a recombinant human factor XIII-A₂ homodimer composed of two factor XIII (FXIII) A-subunits. 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.

TRETEN is manufactured as an intracellular, 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, including hydrophobic interaction and ion exchange chromatography. No human or animal derived products are used in the manufacturing process.

TRETEN is supplied as a sterile, white lyophilized powder in a single use vial. Table 1 and Table 2 list the vial content of reconstituted TRETEN and the diluent, respectively.

Table 1 Content of Reconstituted TRETEN*

Content	Per Vial*	Function
Coagulation Factor XIII A-Subunit (Recombinant)	2000 – 3125 IU	Active substance
Sodium Chloride	8.70 mg	Stabilizer
Sucrose	174.0 mg	Stabilizer
Polysorbate 20	0.30 mg	Surfactant
L-Histidine	9.30 mg	Buffer

* Values are given per 3 mL reconstituted TRETEN.

Table 2 Content of Diluent for Reconstitution of TRETEN

Content	Per Vial	Function
Sterile Water for Injection	3.2 mL	Diluent

After reconstitution with 3.2 mL sterile water for injection, each vial contains 667-1042 IU/mL of recombinant coagulation factor XIII A-subunit. The reconstituted solution has a pH of approximately 8.0. The formulation contains no preservative and must only be administered intravenously.

12 CLINICAL PHARMACOLOGY

12.1 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 [A₂B₂] composed of two FXIII A-subunits and two FXIII B-subunits held together by strong non-covalent interactions. The FXIII A is the catalytic subunit and 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 [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 Ca²⁺. 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 enhance platelet and clot adhesion to injured tissue.

Coagulation Factor XIII A-Subunit (Recombinant) is a protransglutaminase (rFXIII [rA₂] homodimer) and binds to free human FXIII B-subunit resulting in a heterotetramer [rA₂B₂] with a similar half-life to [A₂B₂]. rFXIII has been shown to be activated by thrombin in the presence of Ca²⁺. Activated rFXIII has been shown in dose-dependent manner to increase mechanical strength of fibrin clots, retard fibrinolysis, and rFXIII has been shown to enhance platelet adhesion to the site of injury. After combining with available plasma B-subunits, Coagulation Factor XIII A-subunit (Recombinant) has been shown to have the same pharmacodynamic properties in plasma as endogenous FXIII.

12.2 Pharmacodynamics

A qualitative assay of clot solubility is widely used as an indicator of FXIII deficiency; when performed correctly the test is positive only when the FXIII activity in the sample is close to zero. The results of standard coagulation tests are normal as it is the quality of the clot that is affected. In addition, at present there are no markers that can quantitatively assess the *in vivo* pharmacodynamics of FXIII.

12.3 Pharmacokinetics

Steady State in Patients (ages 7-58 years old) with Congenital Factor XIII Deficiency

In 23 patients with congenital FXIII A-subunit deficiency, the pharmacokinetics of rFXIII were evaluated over a dosing interval of 28 days during steady state.

The pharmacokinetic parameters based on baseline (trough) adjusted FXIII activity (Berichrom assay) values are shown in Table 3.

Table 3 Pharmacokinetic parameters based on baseline (trough) adjusted FXIII activity

Parameters	Mean (SD)
C _{ss, max} (IU/mL)	0.71 (0.17)
C _{ss, min} (IU/mL)	0.05 (0.05)
AUC _(0-inf) (IU*h/mL)	128.3 (40.5)
Clearance (mL/h/kg)	0.33 (0.11)
Half-life (days)	5.1 (2.6)
V _{ss} (mL/kg)	65.9 (26.9)
MRT (days)	7.9 (3.4)

At steady state, the pharmacokinetics of rFXIII are comparable with the single dose pharmacokinetics of rFXIII.

Pediatric (Ages 1 to < 6 Years Old)

In a pharmacokinetic trial six children with congenital FXIII A-subunit deficiency were administered a single intravenous dose of 35 IU/kg. The pharmacokinetic parameters based on baseline (trough) adjusted FXIII activity (Berichrom assay) values are shown in Table 4. No dose adjustment is needed for pediatric patients as there is no influence of age on the pharmacokinetics of TRETEN.

Table 4 The pharmacokinetic parameters based on baseline (trough) adjusted FXIII activity

Parameters	Mean (SD)
C _{max} (IU/mL)	0.48 (0.14)
AUC _(0-inf) (IU*h/mL)	107.8 (32.2)
Clearance (mL/h/kg)	0.41 (0.20)
Half-life (days)	7.1 (1.9)
V _{ss} (mL/kg)	61.2 (41.0)
MRT (days)	7.5 (4.8)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of TRETEN, or studies to determine the effects of TRETEN on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of TRETEN was completed and suggests minimal carcinogenic risk from product use.

13.2 Animal Toxicology and/or Pharmacology

Exaggerated pharmacologic effects, including general thrombosis, ischemic necrosis and mortality were observed in nonclinical studies with TRETEN and non-proteolytically activated recombinant FXIII at a dose of 1670 IU/kg, i.e., 48 times the recommended human dose of 35 IU/kg.

In a monkey cardiovascular safety pharmacology model evaluating the combination of excessive doses of TRETEN (585 IU/kg, 17 times the expected human dose) in combination with rFVIIa (1000 mcg/kg, 11 times the expected human dose), one of the twelve monkeys died 4 hours after treatment due to thrombosis. Procoagulant risk factors, including 6 indwelling catheters per monkey and the induction of anesthesia, may have complicated the study results. It is unclear whether the mortality was related to the overdose of one or both products, or a specific interaction between them. Nonclinical and clinical studies with the combination of TRETEN and rFVIIa at recommended human doses have not been performed.

14 CLINICAL STUDIES

To establish the efficacy of TRETEN for the prevention of bleeding in patients with congenital FXIII A-subunit deficiency, a multi-center, open-label, non-controlled trial was conducted for 52 weeks in forty-one (41) subjects \geq 6 years. All subjects received monthly doses of TRETEN at 35 IU/kg. Bleeding episodes that required treatment with a FXIII-containing product were observed to evaluate the efficacy of monthly replacement therapy with TRETEN on prevention of bleeding episodes.

Subjects with congenital FXIII A-subunit deficiency confirmed by genotyping were included. Subjects who before entering the trial had received regular replacement therapy were to have initiated regular replacement therapy at least 6 months prior to screening and were to have a documented history of at least one treatment-requiring bleeding episode before initiation of regular replacement therapy or a documented family history of FXIII congenital deficiency. Subjects who before entering the trial had only received on-demand treatment were to have a documented history of at least two treatment-requiring bleeding episodes within 12 months of the screening visit. Severe bleeders as defined by a documented history of \geq 2 treatment requiring bleedings per year during regular FXIII replacement therapy were excluded.

During the prophylaxis treatment period with TRETEN (434 subject months), five bleeding episodes treated with FXIII-containing products were observed in four subjects. All five were associated with trauma. When calculated for all 41 subjects, this translated into a mean annual rate of bleeding episodes that required treatment of 0.14 [95% CI:0.058-0.332] per subject year, which was statistically significantly lower than the historic bleeding rate of 1.68 per subject year for on-demand treatment. The age-adjusted rate of bleeding episodes that required treatment during the TRETEN treatment period was 0.05 [95% CI: 0.0094 - 0.2501] per subject year with a model-based estimate corresponding to the mean age of 26.4 years. The mean annual bleeding rate in patients below 18 years of age was higher compared to that in adults (0.362 versus 0.040 bleeds/subject/year). Table 5 below lists the estimated bleeding rates by age.

Table 5 Estimated Bleeding Rates by Age

Group	N	Estimated Bleeding Rate (bleeds/subject/year)	95% CI	Historical Control Group Estimated Bleeding Rate (bleeds/subject/year)
All	41	0.138	[0.058; 0.332]	1.68
< 18 years	15	0.362	[0.136; 0.963]	2.00
\geq 18 years	26	0.040	[0.006; 0.283]	1.59

Thirty-four (34) of the 41 subjects and an additional 21 new subjects were enrolled in an ongoing second trial. During a total treatment period of 107.5 subject years (mean of 1.95 years per subject), 5 subjects experienced 6 bleeds that required treatment with a FXIII-containing product. The mean annual rate of bleeding episodes that required treatment was determined to be 0.056 per subject year. The age-adjusted rate of bleeding episodes that required treatment during the TRETEN treatment period was 0.022 per subject year [95% CI:0.0045; 0.1023] with a model-based estimate corresponding to a mean age of 29.5 years. The annual mean bleeding rate in patients below age 18 was higher

compared to that in adults (0.127 versus 0.026 bleeds/subject/year) with some overlap of the respective 95% confidence intervals. Table 6 lists the estimated bleeding rates by age.

Table 6 Estimated Bleeding Rates by Age

Group	N	Estimated Bleeding Rate (bleeds/subject/year)	95% CI
All	55	0.056	[0.025; 0.124]
< 18 years	16	0.127	[0.048; 0.339]
≥ 18 years	39	0.026	[0.007; 0.105]

15 REFERENCES

1. Inbal, A., et.al.:Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency, *Blood*. 2012;119(22): 5111-5117

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TRETTEN, Coagulation Factor XIII A-Subunit (Recombinant), is supplied as a white, lyophilized powder in single-use vial along with the diluent (Sterile Water for Injection) vial.

The actual amount of TRETTEN in international units (IU) is stated on each carton and vial. TRETTEN and the sterile water vials provided in the package are not made with natural rubber latex.

Presentation	Carton NDC Number	Components NDC Number
2000 - 3125 IU	0169-7013-01	<ul style="list-style-type: none"> • TRETTEN Single-use Vial [NDC 0169-7113-11] • Sterile Water for Injection Vial [NDC 0169-7000-93]

Storage and Handling

- Store refrigerated at 2°C – 8°C (36°F – 46°F) prior to reconstitution. TRETTEN is stable until the expiration date on the carton and vial label. Do not freeze. Store protected from light.
- Use reconstituted TRETTEN within 3 hours.
- If the reconstituted product is not used immediately, store the solution refrigerated or at room temperature not to exceed 25°C (77°F) for up to 3 hours following reconstitution.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Discuss the signs and symptoms of allergic hypersensitivity reactions, such as urticaria, rash, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of TRETTEN [*see Warnings and Precautions (5.1)*].
- Discuss signs and symptoms of thrombosis, such as limb or abdomen swelling and/or pain, chest pain, shortness of breath, loss of sensation or motor power, altered consciousness, vision, or speech [*see Warnings and Precautions (5.2)*].

- Inform patients that breakthrough bleeding may be the sign and symptom of inhibitor formation [*see Warnings and Precautions (5.3)*].

License Number: 1261

TRETTEN[®] is covered by US Patent No. 7,220,556 and other patents pending.

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