PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ZONOVATE®

Antihemophilic Factor (Recombinant, B-Domain Truncated)

turoctocog alfa

Lyophilized Powder

250, 500, 1000, 1500, 2000 and 3000 IU/vial

Intravenous injection

ATC code: B02BD02
Blood Coagulation Factor VIII

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	03/2021

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZONOVATE® (Antihemophilic Factor (Recombinant, B-Domain Truncated)), is indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency or classic hemophilia) for:

- Treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

ZONOVATE® is not indicated for the treatment of von Willebrand disease.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ZONOVATE® have been demonstrated in pediatric patients from 1 to <18 years old [see WARNINGS AND PRECAUTIONS/ Special Populations/ Pediatrics (7.1.3) and CLINICAL TRIALS (14.0)].

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies with ZONOVATE® did not include patients aged more than 65 years to determine whether they respond differently from younger subjects. As with any patient receiving ZONOVATE®, dose selection for an elderly patient should be individualized.

2 CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation (including hamster protein), or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging (5.0).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- For intravenous use after reconstitution only.
- ZONOVATE® treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- The number of units of Factor VIII administered is expressed in International Units (IU), which is related to the current WHO standard for Factor VIII products. The activity of Factor VIII in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for Factor VIII in plasma).
- One IU of Factor VIII activity is equivalent to that quantity of Factor VIII in one mL normal human plasma. The calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

  Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL)

- The dosage and duration of the substitution therapy depend on the severity of the Factor VIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.
- The amount of ZONOVATE® to be administered and frequency of administration should always be oriented to the clinical effectiveness in the individual case.
- When an inhibitor is present, the dosage requirement for ZONOVATE® is extremely variable and the dosage can be determined only by the clinical response.

3.2 Recommended Dose and Dosage Adjustment

Treatment and Control of Bleeding Episodes

A guide for dosing ZONOVATE® for the treatment and control of bleeding episodes is provided in Table 1-1. Dosing should aim at maintaining a plasma Factor VIII activity level at or above the plasma levels (in % of normal or IU/dL) outlined in Table 1-1.

Table 1-1: Dosing for Treatment and Control of Bleeding Episodes

Degree of Hemorrhage	Factor VIII level required (IU/dL or % of normal)	Frequency of doses (hours)/ Duration of therapy (days)
Minor Early hemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12 to 24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved
Moderate More extensive hemarthrosis, muscle bleeding or hematoma	30-60	Repeat injection every 12-24 hours for 3-4 days or more until pain and acute disability are resolved
Major Life threatening hemorrhages	60-100	Repeat injection every 8 to 24 hours until threat is resolved

Perioperative Management

A guide for dosing ZONOVATE® during surgery (perioperative management) is provided in Table 1-2. Consideration should be given to maintaining a plasma Factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1-2.

Table 1-2: Dosing for Perioperative Management

Type of surgical procedure	Factor VIII level required (IU/dL or % of normal)	Frequency of doses (hours)/ Duration of therapy (days)
Minor surgery Including tooth extraction	30-60	Repeat every 24 hours, at least 1 day, if needed until healing is achieved
Major surgery	80-100 (pre-and post-operative)	Repeat injection every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30% to 60% (IU/dL)

During the course of treatment, appropriate determination of Factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma Factor VIII activity) is indispensable. Individual patients may vary in their response to Factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Routine Prophylaxis

A guide for dosing ZONOVATE® for routine prophylaxis is included below in Table 1-3.

Table 1-3: Dosing for Routine Prophylaxis

Patient Population	Factor VIII Dose Required (IU/kg)	Frequency of Doses (days)
Adults and adolescents (≥ 12 years)	20-50	3 times weekly
	20-40	Every other day
Children (<12 years)	25-60	3 times weekly
	25-50	Every other day

Immune Tolerance

Factor VIII products have been administered to patients on a high dose schedule in order to induce immune tolerance to Factor VIII, which resulted in disappearance of the inhibitor activity. There is currently no consensus among treaters to the optimal treatment schedule.

3.3 Administration

- The recommended infusion rate for ZONOVATE® is 1–2 mL/min. The rate should be determined by the patient's comfort level.
- Do not mix ZONOVATE® with any other intravenous infusions or medications.

Injecting ZONOVATE® via needleless connectors for intravenous (IV) catheters

The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

Caution: The MixPro® prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use that come with the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 mL sterile luer-lock plastic syringe.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

For detailed instructions on how to administer ZONOVATE® refer to the PATIENT MEDICATION INFORMATION section of the Product Monograph.

3.4 Reconstitution

Table 1-4: Reconstitution

Vial Size	Volume of Solvent to be Added to Vial	Approximate Concentration After Reconstitution
250 IU/vial	4 mL	62.5 IU/mL
500 IU/vial	4 mL	125 IU/mL
1000 IU/vial	4 mL	250 IU/mL
1500 IU/vial	4 mL	375 IU/mL
2000 IU/vial	4 mL	500 IU/mL
3000 IU/vial	4 mL	750 IU/mL

- ZONOVATE® is recommended to be used immediately after it has been reconstituted.
- If you cannot use the reconstituted ZONOVATE® solution immediately, it must be used within 24 hours when stored in the refrigerator at 2°C - 8°C, within 4 hours when stored at room temperature ≤ 30°C, or within 2 hours when stored between 30°C and 40°C. Store the reconstituted product in the vial, with the vial adapter and the syringe still attached.
- Do not freeze reconstituted ZONOVATE® solution or store it in syringes. Keep reconstituted ZONOVATE® solution out of direct light.
- After reconstitution, the solution appears as a clear or slightly opalescent (slightly unclear) solution. Do not use solutions that are cloudy or have deposits.

3.5 Missed Dose

Double doses are generally not required to compensate for forgotten individual doses. Patients should be advised to proceed immediately with a regular administration of ZONOVATE® and to continue treatment at regular intervals as required.

4 OVERDOSAGE

No symptoms associated with overdose were reported.

For management of a suspected drug overdose, contact your hemophilia treatment centre or your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1-5: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Lyophilized powder and solvent for solution for injection 250, 500, 1000, 1500, 2000 and 3000 IU/vial	Powder Calcium chloride dihydrate, L-histidine, L-methionine, polysorbate 80, sodium chloride, sucrose Solvent Sodium chloride, water for injections

ZONOVATE® is supplied as a white, lyophilized powder in a single-use vial. ZONOVATE® is available in strengths of 250, 500, 1000, 1500, 2000 or 3000 IU/vial.

The solvent for reconstitution of ZONOVATE® is 0.9% sodium chloride solution and is supplied as a clear colorless solution in a prefilled syringe.

The ZONOVATE® package contains 1 vial of ZONOVATE® and 1 MixPro® prefilled solvent syringe with sterile vial adapter, which serves as a needleless reconstitution system.

Each ZONOVATE® package contains:

- 1 glass vial (type I) with ZONOVATE® powder and chlorobutyl rubber stopper
- 1 sterile vial adapter (with 25 micrometer filter) for reconstitution
- 1 prefilled syringe containing 4 mL of solvent with a backstop (polypropylene), a rubber plunger (bromobutyl), and a tipcap with a stopper (bromobutyl)
- 1 plunger rod (polypropylene)

After reconstitution, ZONOVATE® contains the following non-medicinal ingredients:

Contents	Per vial	Function
Sodium chloride*	18 mg/mL	Stabiliser
L-histidine	1.5 mg/mL	Buffering agent
Sucrose	3 mg/mL	Bulking agent
Polysorbate 80	0.1 mg/mL	Surfactant
L-methionine	0.055 mg/mL	Antioxidant
Calcium chloride dihydrate	0.25 mg/mL	Stabiliser

* The amount of sodium chloride originates from the formulation and from the solvent (0.9% Sodium Chloride Solution) used for reconstitution.

6 DESCRIPTION

Antihemophilic Factor (Recombinant, B-Domain Truncated), turoctocog alfa, is a purified protein that has 1445 amino acids with an approximate molecular mass of 166 kDa (calculated excluding post-translational modifications). The molecule has been designed as a polypeptide containing a heavy chain of 87 kDa and a light chain of 79 kDa, held together by non-covalent interactions. In wild type Factor VIII the heavy chain contains varying lengths of B-domain, which in turoctocog alfa is a truncated B-domain with 21 amino acid residues. Six potential sites for tyrosine sulfation have been shown to be sulfated in the turoctocog alfa molecule. The tyrosine sulfation site corresponding to Tyr1680 in the (endogenous full length) Factor VIII,

which is important for the binding to von Willebrand Factor, has been found to be fully sulfated in the turoctocog alfa molecule.

ZONOVATE® is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. In culture, the CHO cell line expresses recombinant Factor VIII (rFVIII) into the cell culture medium. The cell culture and purification processes used in the manufacture of ZONOVATE® employ no additives of human or animal origin. The rFVIII is purified from the cell culture medium using a series of chromatography steps. The purification process includes an immunoaffinity chromatography step in which a monoclonal antibody directed against Factor VIII is employed to selectively isolate the rFVIII from the medium. The process also includes a size exclusion chromatography step to separate High Molecular Weight Protein from rFVIII. The production process includes a detergent treatment step and a dedicated 20 nanometer virus filtration step. The rFVIII synthesized by the CHO cells has the same biological effects on clotting as native human Factor VIII.

ZONOVATE® is formulated as a sterile, non-pyrogenic, white or slightly yellow powder for intravenous injection. Each vial of ZONOVATE® is labeled with the rFVIII activity expressed in IU determined using the European Pharmacopoeia chromogenic assay, using a reference material calibrated against a World Health Organization (WHO) International Standard for Factor VIII Concentrates. One IU, as defined by the WHO standard for human FVIII, is approximately equal to the level of FVIII activity in 1 mL of fresh pooled human plasma.

7 WARNINGS AND PRECAUTIONS

General
Identification of the clotting defect as Factor VIII deficiency is essential before the administration of ZONOVATE®. No benefit may be expected from this product in treating other coagulation factor deficiencies.

Carcinogenesis and Mutagenesis
Long-term studies in animals to evaluate the carcinogenic potential of ZONOVATE®, or studies to determine the effects of ZONOVATE® on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of ZONOVATE® was completed, and no carcinogenic risk from product use has been identified.

Driving and Operating Machinery
ZONOVATE® has no influence on the ability to drive and use machines.

Immune
Hypersensitivity
As with any intravenous protein product, allergic type hypersensitivity reactions are possible with ZONOVATE®. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of ZONOVATE® immediately and contact their physician and/or seek emergency medical treatment. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of anaphylactic shock, standard medical treatment should be implemented.

Inhibitors
The formation of neutralizing antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the Factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay.

The risk of developing inhibitors is correlated to the exposure to Factor VIII, the risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre, posing less of a risk of insufficient clinical response than high titre inhibitors.

All patients treated with ZONOVATE® should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory testing (see Monitoring and Laboratory Tests Section).

Monitoring and Laboratory Tests
Patients should be monitored for the development of Factor VIII inhibitors. If the expected plasma levels of Factor VIII activity are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a Factor VIII inhibitor is present. In patients with high levels of inhibitors, Factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with hemophilia and Factor VIII inhibitors.

When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining Factor VIII activity in blood samples, plasma Factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also, there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Peri-Operative Considerations
ZONOVATE® is indicated in the perioperative management of patients with hemophilia A. Careful control of replacement therapy is important, especially in cases of major surgery or life threatening hemorrhages. There is limited experience of surgery in pediatric patients.

Reproductive Health: Female and Male Potential
Fertility
It is not known if ZONOVATE® can affect fertility.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with ZONOVATE®. Based on the rare occurrence of hemophilia A in women, experience regarding the use of Factor VIII during pregnancy is not available. Therefore, ZONOVATE® should only be used during pregnancy if clearly indicated.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age)

Children have a shorter half-life and lower recovery of Factor VIII than adults. Because clearance (based on per kg body weight) has been demonstrated to be higher in the pediatric population, higher or more frequent dosing based on body weight may be needed [see ACTION AND CLINICAL PHARMACOLOGY/ Pharmacokinetics (10.3)].

7.1.4 Geriatrics

Geriatrics (>65 years of age)

Clinical studies of ZONOVATE® did not include patients above 65 to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In previously treated patients (PTPs) during all clinical studies (3 clinical and 4 pharmacokinetic trials) with ZONOVATE®, a total of 35 adverse reactions were reported in 23 of 242 patients exposed to ZONOVATE®. Of the 35 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in 32 patients from 6 to 12 years of age, 1 in 1 of 24 patients from 12 to <18 years of age, and 32 in 21 of 155 adults (≥18 years). The most frequently reported adverse reactions were injection site reactions (1.2%).

In previously untreated patients (PUPs) aged 0-6 years, a total of 46 adverse reactions were reported in 33 of 60 patients exposed to ZONOVATE® during 1 clinical trial. The most frequently reported adverse reaction was Factor VIII inhibition (44.8%) and pyrexia (3.3%).

Immunogenicity
Patients were monitored for neutralizing antibodies (inhibitors) against Factor VIII, as well as for antibodies against Chinese Hamster Ovaries (CHO) and murine proteins.

FVIII inhibitors:

In PTPs without a history of inhibitors, FVIII inhibitor development was not observed during an accumulated exposure of more than 130,000 EDs (854.9 patient years) in the 3 clinical trials and 4 pharmacokinetic trials. A twenty-two month old child had one positive FVIII inhibitor test (1.3 BU) in the Bethesda assay after fifteen exposure days. However, the result was not confirmed by a second sample taken after an additional five days of exposure. *In vivo* recovery of Factor VIII was normal and no clinical adverse findings were observed in the patient.

In the PUP trial (accumulated exposure of more than 10,000 EDs or 115.4 patient years), FVIII

inhibitor development was observed in 26 of 58 (44.8%) patients. High titre inhibitors defined as a peak titre ≥5 BU accounted for 16 of the 26 inhibitor cases (61.5%) [or for 16 of 58 patients (27.6%)]. Mean time to inhibitor development was 17.5 EDs. High risk genetic mutations (e.g., nonsense, deletions, insertions, inversions) were identified in 92.3% of the 26 cases.

Anti-CHO antibodies:

No clinical adverse findings were observed in relation to anti-CHO antibodies (Ab). Anti-CHO Ab were detected in 19 patients. In two patients, anti-CHO Ab were detected only after treatment, whereas in 6 patients anti-CHO Ab were only detected prior to treatment. In the remaining 11 subjects, Ab were either detected throughout the trial (in 6 subjects), detected only transiently (in 2 subjects), or detected at baseline and end-of trial but undetectable during treatment (in 3 subjects). No data is available in PUPs.

Anti-murine antibodies:

No patients developed *de novo* anti-murine antibodies.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. Table 1-6 summarises the Adverse Drug Reactions from all clinical studies (3 clinical and 4 pharmacokinetic trials) in previously treated patients (PTPs); Table 1-7 summarises the Adverse Drug Reactions from a clinical trial in previously untreated patients (PTPs),

Table 1-6: Summary of Adverse Drug Reactions with a Frequency of ≥ 1% in Clinical Studies in Previously Treated Patients*

	Zonovate n= 242 n (%)
General disorders and administration site conditions Injection site reactions**	3 (1.2)

* Calculated based on total number of unique patients in all clinical studies (242).
** Injection site reactions include: injection site erythema, injection site extravasation and injection site pruritus.

Table 1-7: Summary of Adverse Drug Reactions with a Frequency of ≥ 1% in a Clinical Study in Previously Untreated Patients

	Zonovate n= 60 n (%)
Blood and lymphatic disorder Factor VIII inhibition	29 (48.3)
Gastrointestinal disorders Vomiting	1 (1.7)
General disorders and administration site conditions	

	Zonovate n= 60 n (%)
Pyrexia	2 (3.3)
Catheter site erythema	1 (1.7)
Injury, poisoning and procedural Complications	
Infusion related reaction	1 (1.7)
Investigations	
Anti factor VIII antibody positive	1 (1.7)
Musculoskeletal and connective tissue disorders	
Hemarthrosis	1 (1.7)
Muscle hemorrhage	1 (1.7)
Product issues	
Thrombosis in device	1 (1.7)
Respiratory, thoracic and mediastinal disorders	
Cough	1 (1.7)
Skin and subcutaneous tissue disorder	
Rash	1 (1.7)
Rash erythematous	1 (1.7)
Vascular disorders	
Flushing	1 (1.7)
Thrombophlebitis superficial	1 (1.7)

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

Cardiac disorders: Acute myocardial infarction (0.4%), sinus tachycardia (0.4%)
General disorders and administration site conditions: Pyrexia (0.8%), fatigue (0.4%), feeling hot (0.4%), peripheral swelling (0.4%)
Injury, poisoning and procedural complications: Contusion (0.4%)
Investigations: Hepatic enzymes increased (0.8%), alanine aminotransferase increased (0.4%), aspartate aminotransferase increased (0.4%), heart rate increased (0.4%)
Musculoskeletal and connective tissue disorders: Arthropathy (0.8%), musculoskeletal pain (0.4%), musculoskeletal stiffness (0.4%), pain in extremity (0.4%)
Nervous System Disorders: Burning sensation (0.4%), dizziness (0.4%), headache (0.4%)
Psychiatric disorders: Insomnia (0.4%)
Skin and subcutaneous tissue disorders: Lichenoid keratosis (0.4%), rash (0.4%), skin burning sensation (0.4%)
Vascular disorders: Hyperemia (0.4%), hypertension (0.4%), lymphedema (0.4%)

8.4 Post-Market Adverse Reactions

Overall, the distribution, pattern and type of adverse drug reactions received from post-marketing sources are comparable to the adverse drug reactions from clinical trials. Post-marketing cases of inhibitor development have been reported in both previously untreated patients (PUPs) and previously treated patients (PTPs).

9 DRUG INTERACTIONS

9.1 Overview

No interactions of human coagulation Factor VIII (rDNA) products with other medicinal products have been reported.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ZONOVATE® temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis.

ZONOVATE® contains human coagulation Factor VIII (rDNA), Antihemophilic Factor (Recombinant, B-Domain Truncated), a glycoprotein that has the same structure as human Factor VIII when activated, and post-translational modifications that are similar to those of the plasma-derived molecule.

When infused into a hemophilia patient, Factor VIII binds to endogenous von Willebrand Factor in the patient's circulation. The two constituents of the Factor VIII/von Willebrand Factor complex (i.e. Factor VIII and von Willebrand Factor) have different physiological functions. Activated Factor VIII acts as a co-factor for activated Factor IX, accelerating the conversion of Factor X to activated Factor X. Activated Factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Hemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of bleeding tendencies.

10.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Determination of aPTT is a conventional *in vitro* assay for the biological activity of FVIII. Treatment with ZONOVATE® normalizes the aPTT over the effective dosing period.

10.3 Pharmacokinetics

All pharmacokinetic studies with ZONOVATE® were conducted in previously treated patients with severe hemophilia A (Factor VIII ≤ 1%). Plasma Factor VIII activity was measured using both the one-stage clotting assay and the chromogenic assay.

In a multi-center, multi-national, open-label, single dose pharmacokinetic study, 23 patients with severe hemophilia A received 50 international units/kg of ZONOVATE® intravenously. Two patients were below the age of 18 years (13 and 17 years). The pharmacokinetic parameters for the 20 patients who completed the study are summarized in Table 1-8.

Table 1-8: Single-Dose Pharmacokinetics of ZONOVATE® in Adult and Adolescent Patients with Severe Hemophilia A (Factor VIII ≤ 1%), Clotting Assay and Chromogenic Assay

Parameter	Clotting Assay (N=23)	Chromogenic Assay (N=20)*
	Mean (SD)	Mean (SD)
Incremental Recovery (IU/dL)/(IU/kg)	1.9 (0.4)	2.8 (0.6)
AUC (IU*h/dL)	1364 (414)	1870 (508)
CL (mL/h/kg)	4.04 (1.43)	2.87 (0.80)
$t_{½}$ (h)	10.69 (4.84)	11.96 (9.28)
V_{ss} (mL/kg)	56.11 (13.28)	44.31 (28.17)
C_{max} (IU/dL)	102 (21)	154 (29)
MRT (h)	15.22 (6.24)	16.40 (10.14)

AUC, area under the plasma concentration curve; CL, clearance; $t_{1/2}$, terminal half-life; V_{ss}, apparent volume of distribution at steady state; C_{max}, maximum concentration; MRT, mean residence time.
*Samples for 3 of the 23 patients included in the study were **not** analyzed with the chromogenic assay.

In a separate pharmacokinetic study, 28 pediatric patients with severe hemophilia A (14 patients were below 6 years of age and 14 patients were between 6 to <12 years of age) received a single dose of 50 international units/kg of ZONOVATE®. The pharmacokinetic parameters of ZONOVATE® are summarized in Table 1-9 for both groups.

Table 1-9: Single-Dose Pharmacokinetics of ZONOVATE® in 28 Pediatric Patients with Severe Hemophilia A (FVIII ≤1%), Clotting Assay and Chromogenic Assay

Parameter	Clotting assay		Chromogenic assay	
	0−<6 years	6−<12 years	0−<6 years	6−<12 years
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Incremental Recovery (IU/dL)/(IU/kg)	1.8 (0.7)	2.0 (0.4)	2.2 (0.6)	2.5 (0.6)
AUC (IU*h/dL)	989 (414)	1109 (373)	1221 (438)	1436 (348)
CL (mL/h/kg)	6.26 (3.73)	5.02 (1.67)	4.60 (1.75)	3.70 (1.00)
$t_{½}$ (h)	7.65 (1.84)	8.02 (1.89)	9.99 (1.71)	9.42 (1.52)
V_{ss} (mL/kg)	57.30 (26.75)	46.82 (10.62)	55.79 (23.71)	41.23 (6.00)
C_{max} (IU/dL)	100 (58)	107 (35)	112 (31)	125 (27)
MRT (h)	9.65 (2.46)	9.91 (2.57)	12.09 (1.88)	11.61 (2.32)

AUC, area under the plasma concentration curve; CL, clearance; $t_{1/2}$, terminal half-life; V_{ss}, apparent volume of distribution at steady state; C_{max}, maximum concentration; MRT, mean residence time.

Some variation was observed in the pharmacokinetic parameters of ZONOVATE® between pediatric and adult patients. The higher CL and the shorter t½ seen in pediatric patients compared to adult patients with hemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger patients. A single dose pharmacokinetic trial (50 IU/kg) was performed in 35 hemophilia patients (≥18 years of age) in different Body Mass Index (BMI) categories. The pharmacokinetic parameters of Zonovate are summarized in Table 1-10 and Table 1-11.

FVIII activity can be monitored with both the one stage clot and the chromogenic assay after ZONOVATE® administration.

Table 1-10 Single-dose Pharmacokinetics of ZONOVATE® (50 IU/kg) by BMI Classes[a] – Clotting assay – Mean (SD)

Parameter	Underweight	Normal Weight	Overweight	Obese Class I	Obese Class II/III
	N=5	N=7	N=8	N=7	N=7
Incremental Recovery (IU/dL)/(IU/kg)	1.7 (0.2)	2.0 (0.2)	2.4 (0.4)	2.3 (0.3)[b]	2.6 (0.3)
AUC (IU*h/dL)	1510 (360)	1920 (610)	1730 (610)	2030 (840)	2350 (590)
CL (mL/h/kg)	3.91 (0.94)	3.20 (1.00)	3.63 (1.24)	3.37 (1.79)	2.51 (0.63)
$t_{½}$ (h)	11.3 (2.0)	11.7 (3.5)	9.4 (2.9)	11.2 (3.5)	11.1 (2.7)
V_{ss} (mL/kg)	56.8 (5.4)	44.8 (6.5)	39.6 (6.0)	42.0 (9.0)	35.0 (4.6)
C_{max} (IU/dL)	100 (11)	121 (10)	144 (26)	140 (21)	161 (32)
MRT (h)	15.1 (3.0)	15.3 (4.8)	11.9 (3.7)	14.4 (4.6)	14.6 (3.7)

[a] BMI groups: Underweight: BMI <18.5 kg/m^2, Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obese class I: BMI 30-34.9 kg/m^2, Obese class II/III: BMI ≥35 kg/m^2.
[b] Based on 6 patients only.
MRT: mean residence time.

Table 1-11 Single-dose Pharmacokinetics of ZONOVATE® (50 IU/kg) by BMI Classes[a] – Chromogenic assay – Mean (SD)

Parameter	Underweight	Normal Weight	Overweight	Obese Class I	Obese Class II/III
	N=5	N=7	N=9	N=7	N=7
Incremental Recovery (IU/dL)/(IU/kg)	2.2 (0.4)	2.9 (0.3)	3.0 (0.5)	3.2 (0.5)	3.5 (0.5)
AUC (IU*h/dL)	1860 (700)	2730 (860)	2310 (1020)	2780 (1210)	3050 (730)
CL (mL/h/kg)	3.28 (0.87)	2.25 (0.73)	2.84 (1.09)	2.58 (1.56)	1.94 (0.52)
$t_{½}$ (h)	11.7 (2.4)	11.5 (3.6)	9.7 (3.4)	10.4 (3.2)	10.5 (2.5)
V_{ss} (mL/kg)	49.1 (10.4)	31.2 (4.5)	31.6 (5.8)	28.9 (5.1)	25.7 (4.0)
C_{max} (IU/dL)	138 (29)	185 (24)	194 (31)	200 (33)	227 (32)
MRT (h)	15.5 (3.2)	15.2 (4.9)	12.6 (4.8)	13.5 (4.6)	13.9 (3.7)

[a] BMI groups: Underweight: BMI <18.5 kg/m^2, Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obese class I: BMI 30-34.9 kg/m^2, Obese class II/III: BMI ≥35 kg/m^2.
MRT: mean residence time.

11 STORAGE, STABILITY AND DISPOSAL

Prior to Reconstitution
Store in refrigerator (2°C - 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

ZONOVATE® vials can be stored in the refrigerator (2°C - 8°C) up to the expiration date stated on the label.

During the shelf-life, ZONOVATE® may also be stored at room temperature:

- up to 30°C for a single period not exceeding 12 months
  or
- up to 40°C for a single period not exceeding 3 months

Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Record the date when the product was removed from the refrigerator in the space provided on the product carton.

Do not use ZONOVATE® after the end of the specified room temperature storage period at up to 30°C or 40°C, or after the expiration date stated on the carton, whichever occurs earlier.

After Reconstitution
Chemical and physical in-use stability have been demonstrated for 24 hours when stored in a refrigerator at 2°C – 8°C, 4 hours when stored at room temperature up to 30°C, and 2 hours when stored between 30°C and 40°C.

From a microbiological point of view, ZONOVATE® should be used immediately after reconstitution. If the reconstituted product is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than as stated above, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution should be stored in the vial, with the vial adapter and the syringe still attached.

Discard any unused reconstituted product.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Antihemophilic Factor (Recombinant, B-Domain Truncated)

Chemical name: turoctocog alfa

Molecular formula and molecular mass: Glycoprotein, 166 kDa (calculated excluding post-translational modifications)

Structural formula:

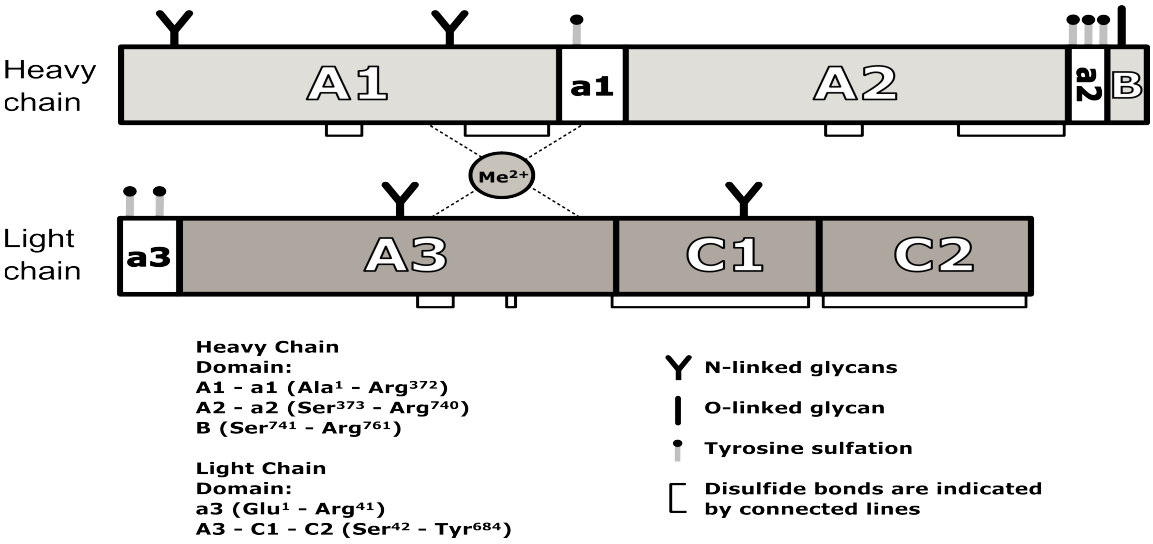


Figure 1: Antihemophilic Factor (Recombinant, B-Domain Truncated) structure showing FVIII domains (A1, a1, A2, a2, B, a3, A3, C1, C2) and post-translational modifications

Physicochemical properties
Antihemophilic Factor (Recombinant, B-Domain Truncated), turoctocog alfa, is produced in Chinese Hamster Ovary (CHO) cells. The designed post translational modifications of the molecule include disulfide bridges, tyrosine sulfations and glycosylations, see Figure 1. Six tyrosine sulfation sites are present in the molecule. The glycosylation sites are N-linked or O-linked and can be fully or partially occupied. Two N-linked glycosylations are present in the light chain and two N-linked glycosylations are present in the heavy chain and the majority of the bi-antennary structures are sialylated. Two O-linked glycosylation sites are present in the light chain and one O-linked glycosylation site is present in the B-domain. The two O-linked glycosylation sites in the light chain are found to be unoccupied in the major part of the molecule and are therefore not shown in Figure 1.

Product Characteristics
ZONOVATE® is a third generation Factor VIII product and is inherently free from the risk of transmission of human blood-borne pathogens, such as human immunodeficiency virus (HIV),

hepatitis viruses and parvovirus, because it is not purified from human blood and is manufactured from a well-characterized cell line in the absence of human- or animal-derived materials. The process also includes a size exclusion chromatography step to separate High Molecular Weight Protein from rFVIII, which leads to a high purity active product. To further enhance the viral safety profile and provide additional assurance to the hemophilia A community, the production process includes a detergent treatment step and a dedicated 20 nanometer virus filtration step. The purified turoctocog alfa is contained in a clear and colourless solution. As turoctocog alfa is a mixture of different glycoforms, it does not possess a distinct pI value. At pH of 4.5 and below, precipitation is observed. At pH of 5.7 and above, full solubility has been observed. However, at pH values above 7.5 degradation occurs.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 2-1: Trial Design and Study Demographics in Patients with Severe Hemophilia A

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number	Mean age (Range)*	Gender
Trial 3543 Pivotal Trial	A multi-centre, open-label, non-controlled trial in prevention and treatment of bleeds in PTPs Sub-Trial Prevention and treatment of bleeding during surgical procedures	*Preventive* 20−50 IU/kg 3 times weekly or 20−40 IU/kg every second day *Treatment of acute bleeds* At investigator's discretion. Target FVIII recovery >0.5 IU/mL. *Surgery* At investigator's discretion. Target FVIII trough activity >0.5 IU/mL. Doses according to local standard practice at the treatment centre.	24 adolescents and 126 adults Surgery 9 adolescents or adults	Mean = 28 years Range = 12 to 60 years	Male
Trial 3545 Pediatric Trial	A multi-centre, open-label, non-controlled trial in PTPs	*Preventive* 25−60 IU/kg 3 times weekly or 25−50 IU/kg every second day *Treatment of acute bleeds* At the investigator's discretion. Target FVIII recovery >0.5 IU/mL	63 pediatrics (below 12 years of age)	Mean = 6 years Range = 1 to 11 years	Male
Trial 3568 Extension Trial of 3543 and 3545	Safety and efficacy in prevention and on-demand treatment of bleeding Sub-trial Prevention and treatment of bleeding during surgical procedures	*Preventive* 20−60 IU/kg 3 times weekly or 20−50 IU/kg every second day *Less frequent preventive* 40−60 IU/kg every third day or twice weekly *Treatment of acute bleeds* At the investigator's discretion. Target FVIII recovery >0.5 IU/mL	55 pediatrics, 23 adolescents and 135 adults Surgery 14 adolescents or adults and 3 pediatrics	Mean = 23 years Range = 1 to 60 years	Male

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number	Mean age (Range)*	Gender
		Surgery At the investigator's discretion. Target FVIII trough activity >0.5 IU/mL. Doses according to local standard practice at the treatment centre			
Trial 3809 Previously Untreated Patients	A multi-centre, non-randomized, open-label trial in PUPs	*Preventive* A starting dose between 15−50 IU/kg once weekly with gradual increase to: 20−60 IU/kg 3 times weekly or 20−50 IU/kg every second day *Treatment of acute bleeds* At the investigator's discretion. Target FVIII recovery >0.5 IU/mL	60 pediatrics	Mean = 10 months Range = 0 to 42 months	Male

* At inclusion in the trial.

Four multi-centre, open-labelled, non-controlled trials have been conducted to evaluate the safety and efficacy of ZONOVATE® in the prevention and treatment of bleeds and during surgery in patients with severe hemophilia A (Factor VIII activity ≤1%). An overall assessment of efficacy was performed by the patient (for home treatment) or study site investigator (for treatment under medical supervision) using a four-point scale of excellent, good, moderate, or none. If the hemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the hemostatic response was rated as moderate, or none, or missing, the treatment was considered a failure.

Three of these trials were performed in previously treated patients (PTPs) without a history of FVIII inhibitors, and included one pivotal trial in 150 adults and adolescents (trial 3543), one trial in 63 pediatric patients (trial 3545) and one safety extension trial in 213 patients (trial 3568). Patients received routine prophylaxis 3 times weekly or every second day (standard prevention). In the final year of trial 3568, patients were allowed to follow a less frequent preventive regimen (every third day or twice weekly) based on patient's clinical response and bleeding phenotype. For the treatment of breakthrough bleeds or on-demand therapy and surgery, dosage was at the investigator's discretion. Two trials included a surgery sub-trial part for patients who during the course of the trial needed to undergo a major or minor surgical procedure requiring at least 7 days of daily Factor VIII treatment, including the day of surgery.

These 3 trials included 238 exposed patients: 24 adolescents between 12 and 18 years, and 151 adult patients between 18 and 60 years old with ≥150 exposure days, and 63 pediatric patients (31 aged 1 to < 6 and 32 aged 6 to < 12) with ≥50 exposure days. A total of 188 out of 238 previously treated patients continued in the safety extension trial 3568. Of the 238 patients, 231 received standard preventive treatment and 27 patients received a less frequent preventive treatment at some point during the trials. There were 25 patients (3 children, 2 adolescents and 20 adult patients) who underwent surgery in trials 3543 and 3568.

The fourth trial (trial 3809) evaluated the incidence of FVIII inhibitors (≥0.6 BU) in 60 previously untreated patients (PUPs) below 6 years of age following 100 EDs. Patients were gradually exposed to ZONOVATE®, at a starting dose of 15−50 IU/kg BW once weekly with increases to

20−50 IU/kg BW every second day or 20−60 IU/kg BW three times weekly. Assessment for hemostatic efficacy as a secondary endpoint was performed in the same way as for PTPs.

14.2 Study Results

Overall clinical efficacy with regards to prophylaxis and treatment of bleeds with ZONOVATE® was established in children and adults.

In the three trials in PTPs (studies 3543, 3545 and 3568) during standard preventive treatment, a majority of bleeds were resolved with 1−2 infusions of ZONOVATE®, including 90.5% in adults and adolescents and 86.9% in pediatrics.

Routine Prophylaxis
A total of 231 PTPs received ZONOVATE® for routine prophylaxis across the 3 clinical trials. For prophylactic dosing regimens see Table 2-1. The majority of the patients (>80%) were treated with the three times per week regimen.

Table 2-2: Annualized Bleeding Rate (ABR) and Dose per Patient used for Standard Prevention

	Younger children (0−<6 years)	Older children (6−<12 years)	Adolescents (12−<18 years)	Adults (≥18 years)	Total
Number of patients	31	32	24	144	231
Trial 3543 (Adults & Adolescents)					
Number of patients	-	-	24	126	150
Mean ABR*	-	-	5.5	6.7	6.5
Median ABR (IQR)	-	-	4.0 (6.2)	3.7 (9.0)	3.9 (8.7)
Dose (IU/kg BW)					
Mean (SD)	-	-	23.3 (6.4)	24.6 (6.6)	24.4 (6.6)
Min ; Max	-	-	18.3 ; 53.6	12.8 ; 97.4	12.8 ; 97.4
Trial 3545 (Pediatrics)					
Number of patients	31	32	-	-	63
Mean ABR*	4.8	5.9	-	-	5.4
Median ABR (IQR)	3.0 (6.3)	3.7 (8.9)	-	-	3.1 (8.7)
Dose (IU/kg BW)					
Mean (SD)	37.8 (8.8)	35.8 (8.9)	-	-	36.8 (8.9)
Min ; Max	3.4 ; 73.9	3.2 ; 59.7	-	-	3.2 ; 73.9
Trial 3568 (Extension)					
Number of patients[+]	27	28	23	128	206
Mean ABR*	1.9	2.9	1.9	2.6	2.5
Median ABR (IQR)	1.1 (2.8)	1.6 (3.8)	1.6 (2.3)	1.4 (3.0)	1.4 (2.9)
Dose (IU/kg BW)					
Mean (SD)	41.8 (7.9)	38.2 (9.3)	28.7 (9.1)	28.9 (8.2)	32.2 (9.9)
Min ; Max	3.9 ; 196.3	3.9 ; 62.5	17.4 ; 73.9	12.0 ; 69.9	3.9 ; 196.3

BW: Body weight, SD: Standard deviation. IQR: Interquartile range.
*Mean bleeds/patient/year, estimated from a Poisson model allowing for over-dispersion.
[+] Of the total 213 patients dosed in the trial, 206 were treated with a standard preventive regimen.

Control of Breakthrough Bleeding Episodes

In PTPs, a total of 499 bleeds in adolescents and adults (trial 3543) and 126 bleeds in pediatric patients (trial 3545) were reported. An additional 1748 bleeds were reported in the extension (trial 3568, including all age groups) during standard preventive treatment. Traumatic bleeds were more frequent among pediatric patients whereas spontaneous bleeds were more frequent among adolescents and adults. The vast majority of the bleeds were of mild/moderate severity and most frequently localized in articular joints.

In adults and adolescents (trial 3543), bleeds were classified as mild/moderate in 90% of the cases, as severe in 9% of the cases and for the remaining 1%, the classification was not reported. The majority of the bleeds (66.5%) were spontaneous, 24.8% were caused by trauma and 8.6% were of other origin or with missing information. Joints were the most frequent locations, accounting for 75% of the total bleeds.

In the pediatric population (trial 3545), bleeds were classified as mild/moderate in 91% of the cases, as severe in 6% of the cases and for the remaining 3%, the classification was not reported. The majority of the bleeds (67%) were caused by a trauma, 32% were spontaneous and for the remaining 1%, the cause was not reported. The proportion of bleeds caused by trauma was 83% among the small children and 55% among the older children. Joints were the most frequent locations of bleeds, accounting for 47%.

In the extension trial (trial 3568), bleeds were classified as mild/moderate in 87% of the cases and as severe in 13% of the cases. The majority of the bleeds (55%) were spontaneous and 45% were caused by trauma; however for older children, 27% were spontaneous and 74% were caused by trauma. Joints were the most frequent locations of bleeds, accounting for 75%.

Previously Untreated Patients (PUPs)

In PUPs (trial 3809), 500 bleeds were reported in 57 of 60 patients, with 402 bleeds reported during a preventive regimen and 98 bleeds in those treated for bleeds while waiting to start preventive treatment. The majority of the 500 bleeds were of mild/moderate severity and frequently subcutaneous. Most bleeds (80.6%) were caused by trauma and often (95.4%) classified as mild/moderate. Fourteen (14) of 22 reported severe bleeds involved patients treated for a bleed while waiting to start preventive treatment.

There were 26 patients (44.8%) who developed FVIII inhibitors following exposure to ZONOVATE® during the trial (see ADVERSE REACTIONS/ Adverse Reaction Overview). Immune Tolerance Induction (ITI) was initiated in 21 of these patients and 18 (86%) patients completed ITI with a negative inhibitor test result.

In non-inhibitor patients gradually receiving a preventive treatment, 79.1% of bleeds were resolved with 1−2 infusions of ZONOVATE®. The success rate for treatment of bleeds during a preventive regimen was 86.1% (see Table 2-3).

Table 2-3: Dose for Treatment of Bleed and Hemostatic Efficacy by Age Group and Trial

	Younger children (0−<6 years)	Older children (6−<12 years)	Adolescents (12−<18 years)	Adults (≥18 years)	Total
Number of patients	90	32	24	144	290
Trial 3543 (Adults & Adolescents)					
Number of patients	-	-	24	126	150
Number of bleeds	-	-	67	432	499
Dose (IU/kg BW)					
Mean (SD)	-	-	24.7 (8.7)	31.4 (10.9)	30.4 (10.8)
Min ; Max	-	-	12.4 ; 48.4	9.8 ; 61.1	9.8 ; 61.1
Success rate* %	-	-	71.6%	82.2%	80.8%
Trial 3545 (Pediatrics)					
Number of patients	31	32	-	-	63
Number of bleeds	53	73	-	-	126
Dose (IU/kg BW)					
Mean (SD)	45.5 (23.7)	37.6 (10.2)	-	-	40.4 (16.6)
Min ; Max	25.9 ; 193.8	25.5 ; 63.6	-	-	25.5 ; 193.8
Success rate* %	96.2%	89.0%	-	-	92.1%
Trial 3568 (Extension Trial)					
Number of patients	27	28	23	128	206
Number of bleeds	204	313	188	1043	1748
Dose (IU/kg BW)					
Mean (SD)	43.7 (9.9)	40.8 (10.6)	30.5 (10.4)	35.9 (13.3)	37.1 (12.7)
Min ; Max	21.4 ; 82.7	24.0 ; 71.4	16.3 ; 76.8	6.4 ; 104.0	6.4 ; 104.0
Success rate* %	91.2%	88.2%	88.8%	90.0%	89.7%
Trial 3809 (Previously Untreated)					
Number of patients	59	-	-	-	59
Number of bleeds	402	-	-	-	402
Dose (IU/kg BW)					
Mean (SD)	44.5 (13.7)	-	-	-	44.5 (13.7)
Min ; Max	16.2 ; 106.5	-	-	-	16.2 ; 106.5
Success rate* %	86.1%	-	-	-	86.1%

BW: Body weight, SD: Standard deviation.
*Success defined as either 'Excellent' or 'Good'.

Table 2-4: Success Rate for Hemostatic Response by Site of Bleed, by Age Group and by Trial

Site of bleed	Younger children (0−<6 years) Bleeds (success rate)[a]	Older children (6−<12 years) Bleeds (success rate)[a]	Adolescents (12−<18 years) Bleeds (success rate)[a]	Adults (≥18 years) Bleeds (success rate)[a]	Total Bleeds (success rate)[a]
Trial 3543 (Adults & Adolescents)					
Joint	-	-	52 (71.2%)	337 (81.6%)	389 (80.2%)
Subcutaneous	-	-	6 (66.7%)	7 (71.4%)	13 (69.2%)
Muscular	-	-	6 (66.7%)	20 (95.0%)	26 (88.5%)
Gastro-intestinal	-	-	0 (-)	3 (66.7%)	3 (66.7%)
Other[b]	-	-	3 (100%)	43 (81.4%)	46 (82.6%)
Missing[c]	-	-	0 (-)	22 (86.4%)	22 (86.4%)
Trial 3545 (Pediatrics)					
Joint	24 (95.8%)	35 (97.1%)	-	-	59 (96.6%)
Subcutaneous	7 (100.0%)	8 (100.0%)	-	-	15 (100.0%)
Muscular	6 (100.0%)	7 (100.0%)	-	-	13 (100.0%)
Mucosal	6 (83.3%)	1 (100.0%)	-	-	7 (85.7%)
Other[b]	10 (100.0%)	20 (75.0%)	-	-	30 (83.3%)
Missing[c]	-	2 (-)	-	-	2 (-)
Trial 3568 (Extension Trial)[d]					
Joint	89 (87.6%)	217 (88.0%)	146 (91.8%)	855 (91.0%)	1307 (90.4%)
Subcutaneous	29 (96.6%)	19 (94.7%)	3 (66.7%)	29 (82.8%)	80 (90.0%)
Muscular	22 (90.9%)	36 (86.1%)	14 (64.3%)	70 (87.1%)	142 (85.2%)
Gastro-intestinal	1 (0.0%)	1 (100.0%)	0 (-)	2 (50.0%)	4 (50.0%)
Mucosal	30 (93.3%)	8 (100.0%)	1 (100.0%)	22 (81.8%)	61 (90.2%)
CNS	0 (-)	0 (-)	1 (100.0%)	0 (-)	1 (100.0%)
Other[b]	33 (97.0%)	30 (83.3%)	23 (87.0%)	63 (88.9%)	149 (89.3%)
Missing[c]	0 (-)	2 (100.0%)	0 (-)	2 (50.0%)	4 (75.0%)
Trial 3809 (Previously Untreated)[e]					
Joint	88 (84.1%)	-	-	-	88 (84.1%)
Subcutaneous	256 (86.7%)	-	-	-	256 (86.7%)
Muscular	38 (84.2%)	-	-	-	38 (84.2%)
Gastro-intestinal	1 (100%)	-	-	-	1 (100%)
Mucosal	29 (79.3%)	-	-	-	29 (79.3%)
CNS	5 (80.0%)	-	-	-	5 (80.0%)
Other[b]	83 (95.2%)	-	-	-	83 (95.2%)

[a] Success rate: Number of 'Excellent' or 'Good' hemostatic responses/number of bleeds.
[b] Other: These bleeds included foot, hand, toe and finger bleeds, gum and nose bleeds, cuts, mild head injuries and bleeding related to dental procedures.
[c] Missing: Information on site of bleed has not been provided in the allotted space of the diary.
[d] Bleeds during preventive treatments.
[e] Pooled data for bleeds during preventive and on demand treatment.

Perioperative Management

Two of the original trials included a surgery sub-trial part for patients who during the course of the trial needed to undergo a major or minor surgical procedure requiring at least 7 days of daily Factor VIII treatment, including the day of surgery. A total of 30 surgeries were performed in 25 patients. The majority of the patients undergoing surgery were adults. Hemostatic response was successful in 100% of the surgeries, both during and after surgery.

Table 2-5: Hemostatic Response by Surgical Procedure in the Pivotal Trial and Extension Trial

Description of surgery	Type	Number of surgeries	Hemostatic response[a]	Patient age range (years)[b]
Trial 3543 (Adults & Adolescents)				
Orthopedic surgeries	Major Minor	6 1	Excellent (5) / Good (1) Good	19-36
Non-orthopedic surgeries	-	-	-	-
Dental	Minor	1	Excellent	23
Circumcision	Minor	1	Excellent	14
Trial 3568 (Extension Study)				
Orthopedic surgeries	Major	13	Excellent (7) / Good (6)	24-58
Non-orthopedic surgeries	Major	5	Excellent (3) / Good (2)	10-50
Dental	Minor	1	Excellent	18
Circumcision	Minor	1	Excellent	8
Insertion of port-a-cath	Minor	1	Excellent	8

[a] Hemostatic response during surgery.
[b] Age at time of surgery.

15 NON-CLINICAL TOXICOLOGY

Carcinogenicity, Genotoxicity, Reproductive Toxicity

Studies concerning carcinogenicity, genotoxicity and reproductive toxicity in animals have not been performed.

Table 2-6: Overview of non-clinical Toxicity Studies

Study title	Species	Dose and frequency	Key findings
Single i.v. dose escalation and toxicokinetic study in the male Cynomolgus monkey	Cynomolgus Monkey	Single i.v. dose of 50, 250, 500, 1250, 2500, 5000 IU/kg (each animal received 2 different doses)	All doses were well tolerated.
Repeat dose toxicity			
14 day i.v. administration toxicity study in the rat	Rat	Daily i.v. doses of 0, 50, 250, 1250 IU/kg	Repeat doses were well-tolerated with no evidence of local or systemic toxicity. Antibodies were elicited in the majority of animals at all dose levels following treatment.

Study title	Species	Dose and frequency	Key findings
14 day i.v. toxicity study with a 6 day recovery period	Cynomolgus Monkey	Daily i.v. doses of 0, 50, 1000, 5000 IU/kg	Consistent with the species foreign nature of turoctocog alfa, neutralizing-antibodies developed in the majority of treated animals resulting in increased hemorrhage.
Genotoxicity	Not performed	NA	NA
Carcinogenicity	Not performed	NA	NA
Reproductive and Developmental toxicity studies	Not performed	NA	NA
Juvenile toxicity	Not performed	NA	NA
Local tolerance			
Local tolerance study in Rabbits 4 days after perivenous, intravenous and intraarterial injection	Rabbit	20 IU/kg i.v.; i.a; perivenous	No local toxicity effects were observed

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ZONOVATE®
Antihemophilic Factor (Recombinant, B-Domain Truncated)

Read this carefully before you start taking ZONOVATE® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ZONOVATE®.

What is ZONOVATE® used for?
ZONOVATE® is used to treat and prevent bleeding episodes in patients with hemophilia A.

How does ZONOVATE® work?
In patients with hemophilia A, Factor VIII is missing or not working properly. ZONOVATE® replaces this faulty or missing 'Factor VIII' and helps blood to form clots at the site of bleeding.

What are the ingredients in ZONOVATE®?
Medicinal ingredients: The medicinal ingredient is human coagulation Factor VIII, produced by recombinant DNA technology. Factor VIII is a protein naturally found in the blood that helps it to clot.

Non-medicinal ingredients: calcium chloride dihydrate, L-histidine, L-methionine, polysorbate 80, sodium chloride, sucrose

ZONOVATE® does not contain any human blood or plasma, albumin, preservatives, or added animal or human components in the final product, making it naturally free from the risk of transmission of blood-borne pathogens such as human immunodeficiency virus (HIV), hepatitis viruses, and parvovirus.

ZONOVATE® comes in the following dosage forms:
ZONOVATE® is available in single-dose vials that contain nominally 250, 500, 1000, 1500, 2000 or 3000 International Units (IU) per vial, with a prefilled syringe containing 4 mL 0.9% sodium chloride solution for injection (solvent). After reconstitution with the supplied solvent the prepared solution for injection will have the following concentration:

Vial size	Approximate concentration of ZONOVATE® after reconstitution
250 IU	62.5 IU/mL
500 IU	125 IU/mL
1000 IU	250 IU/mL
1500 IU	375 IU/mL
2000 IU	500 IU/mL
3000 IU	750 IU/mL

Each pack of ZONOVATE® contains a vial with white or slightly yellow powder, a 4 mL prefilled syringe with a clear colourless solution (solvent), a plunger rod and a vial adapter.

Do not use ZONOVATE® if:
You are allergic to the medicinal ingredient, or to any ingredient in the formulation (including hamster protein), or component of the container. If you are not sure, talk to your doctor before using this medicine.

ZONOVATE® is not indicated for treatment of von Willebrand disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZONOVATE®. Talk about any health conditions or problems you may have, including if you:
- Are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or herbal medicines.
- Are pregnant or breast-feeding, or if you think that you may be pregnant or are planning to have a baby.

Other warnings you should know about:
Talk to your doctor if you do not think your bleed is being controlled with the dose you receive, as there can be several reasons for this. Some people using this medicine can develop antibodies to Factor VIII (also known as 'Factor VIII inhibitors'). Factor VIII inhibitors make ZONOVATE® less effective in preventing or controlling bleeding. If this happens you may need a higher dose of ZONOVATE® or a different medicine to control your bleed.

Do not increase the total dose of ZONOVATE® to control your bleed without talking to your doctor. You should tell your doctor if you have been previously treated with Factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

If your bleed does not stop contact your doctor, your hemophilia treatment centre or go to a hospital immediately.

ZONOVATE® can cause some serious side effects including allergic reactions. You will need to be aware of these while you are using ZONOVATE® (see Serious Side Effects table).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZONOVATE®:
There are no known interactions of ZONOVATE® with other medicinal products.

How to take ZONOVATE®:
Treatment with ZONOVATE® will be started by a doctor who is experienced in the care of patients with hemophilia A. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

ZONOVATE® is given as an injection into a vein (intravenously). Please refer to the end of this insert for instructions on how to prepare and administer ZONOVATE®.

Your doctor will calculate your dose for you. This will depend on your weight and what the medicine is being used for.

Usual dose:
Prevention of bleeding

- The usual dose of ZONOVATE® is 20 to 50 International Units (IU) per kg of body weight.
- The injection is given every 2 to 3 days.

Treatment of bleeding

- The dose of ZONOVATE® is calculated depending on your body weight and the Factor VIII levels to be achieved.
- The amount of ZONOVATE® needed will depend on where the bleed is and how severe it is.

Use in children and adolescents
ZONOVATE® can be used in children. In children (below the age of 12) higher doses or more frequent injections may be needed. Children (above the age of 12) and adolescents can use the same dose as adults.

Overdose:

If you think you have taken too much ZONOVATE®, contact your healthcare professional, your hemophilia treatment centre or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you are taking ZONOVATE® to prevent bleeds you should contact your doctor if you have missed a dose and do not know how to compensate for this.

Stopping Treatment:
If you stop using ZONOVATE® you may no longer be protected against bleeding or a current bleed may not stop. Do not stop using ZONOVATE® without talking to your doctor.

What are possible side effects from using ZONOVATE®?
These are not all the possible side effects you may feel when taking ZONOVATE®. If you experience any side effects not listed here, contact your healthcare professional.

If severe, sudden allergic reactions (anaphylactic reactions) occur (very rare), the injection must be stopped immediately. You must contact your doctor immediately if you have one of the following early symptoms:

- difficulty in breathing, shortness of breath or wheezing
- chest tightness
- swelling of the lips and tongue
- rash, hives, wheals or generalised itching
- feeling dizzy or loss of consciousness
- low blood pressure (having pale and cold skin, fast heartbeat)

Severe symptoms, including difficulty in swallowing or breathing and red or swollen face or hands, require prompt emergency treatment.

If you have an allergic reaction, your doctor may change your medicine.

Side effects in patients who have previously been treated with Factor VIII products
Common side effects (may affect up to 1 in 10 people):
- blood tests showing changes in the way the liver functions
- reactions (redness and itching) around the site where you injected the medicine

Uncommon side effects (may affect up to 1 in 100 people):
- feeling tired
- headache
- feeling dizzy
- difficulty sleeping (insomnia)
- fast heartbeat
- increased blood pressure
- rash
- fever
- feeling hot
- stiffness of muscles
- pain in muscles
- pain in legs and arms
- swelling of legs and feet
- joint disease
- bruising

Side effects in children and adolescents
The side effects observed in children and adolescents are the same as observed in adults.

Side effects in patients who have never been previously treated with Factor VIII products

Very common side effects (more than 1 in 10 people):
- formation of neutralizing antibodies to Factor VIII

Common side effects (may affect up to 1 in 10 people):
- flushing of the skin
- inflammation of vein
- bleeding into joint spaces
- bleeding in muscle tissue
- cough
- redness around the site where you placed catheter
- vomiting
- rash
- fever

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Lack of effect: Bleeding does not stop after taking ZONOVATE®		✓	
VERY RARE			
Severe, sudden allergic reactions: Difficulty breathing or swallowing, chest tightness, swelling of lips and tongue, rash, hives, dizziness, pale and cold skin, fast heartbeat, red or swollen face or hands		✓	✓

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 report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:
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 carton, on the vial, on the vial adapter, and on the prefilled syringe labels. The expiry date refers to the last day of that month.

The powder in the vial appears as a white or slightly yellow powder. Do not use the powder if the colour has changed.

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

ZONOVATE® vials can be stored in the refrigerator (2°C – 8°C) up to the expiration date. During the shelf life, the product may also be kept at room temperature up to 30°C for a single period no longer than12 months, **or** up to 40°C for a single period no longer than 3 months.

If you choose to store ZONOVATE® at room temperature:

- Note the date that the product is removed from refrigeration on the carton.
- Do not use after 12 months if stored up to 30°C **or** after 3 months if stored up to 40°C **or** after the expiration date listed on the carton, whichever is earlier.
- Do not return the product to the refrigerator.

After Reconstitution

Once you have reconstituted ZONOVATE® it should be used immediately. If you cannot use the reconstituted solution immediately, it must be used within 24 hours when stored in the refrigerator at 2°C - 8°C, within 4 hours when stored at room temperature up to 30°C, or within 2 hours when stored between 30°C and 40°C. Store the reconstituted product in the vial, with the vial adapter and the syringe still attached.

If not used immediately the medicine may no longer be sterile and could cause infection. Do not store the solution without your doctor's advice.

The reconstituted solution will be clear to slightly opalescent. Do not use this medicine if you notice that it is cloudy or contains visible particles.

If you want more information about ZONOVATE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.novonordisk.ca, or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

Last Revised: APR-14-2021

INSTRUCTIONS ON HOW TO USE ZONOVATE®

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING ZONOVATE®.

ZONOVATE® is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a 0.9% sodium chloride solution for injection. The reconstituted ZONOVATE® must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject ZONOVATE®.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the ZONOVATE® package.

Do not use the equipment without proper training from your doctor or nurse.

Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medication directly into the veins, it is important to **use a clean and germ free (aseptic) technique.** Improper technique can introduce germs that can infect the blood.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it is expired. Use a new package instead. The expiry date is printed on the outer carton, on the vial, on the vial adapter, and on the prefilled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.

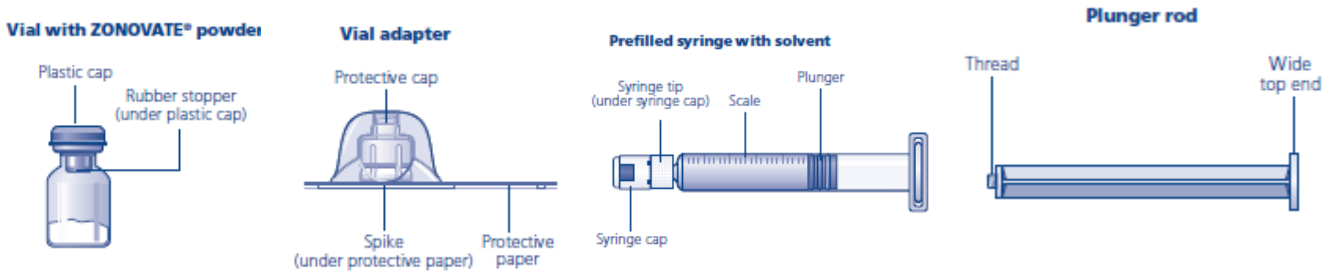
The equipment is for single use only.

Contents

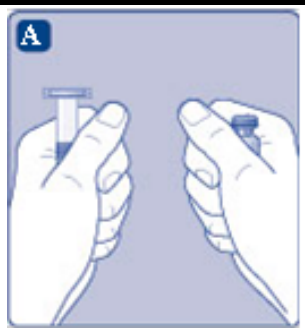
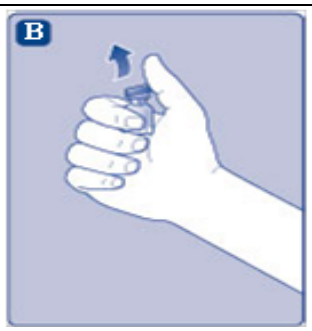
The package contains:
- 1 vial with ZONOVATE® powder
- 1 vial adapter
- 1 prefilled syringe with solvent
- 1 plunger rod (placed under the syringe)

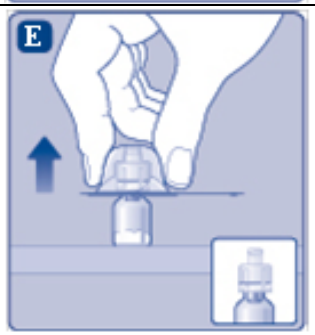
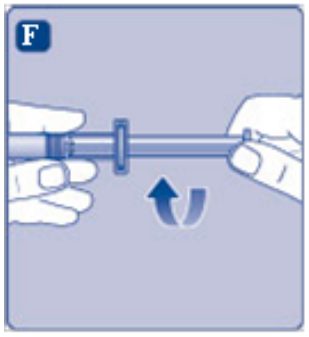
The prefilled solvent syringe with sterile vial adapter, together serve as a needleless reconstitution system named the MixPro®.

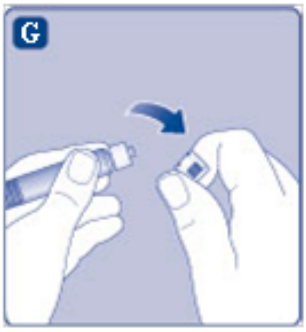
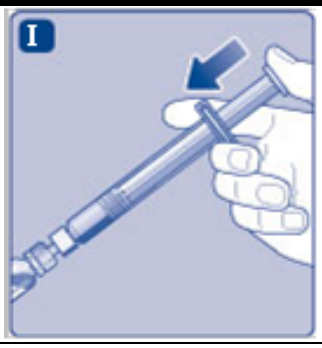
Overview



1. Prepare the Vial and Syringe

Step A		**Take out the number of ZONOVATE® packages you need.** **Check the expiry date.** **Check the name, strength and colour** of the package, to make sure it contains the correct product. **Wash your hands** and dry them properly using a clean towel or air dry. Take the vial, the vial adapter and the prefilled syringe out of the carton. **Leave the plunger rod untouched in the carton.** **Bring the vial and the prefilled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands. **Do not use any other way to heat** the vial and prefilled syringe.
Step B		**Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not use the vial.** **Wipe the rubber stopper with a sterile alcohol swab** and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible. **Do not touch the rubber stopper with your fingers as this can transfer germs.**

2. Attach the Vial Adapter		
Step C		**Remove the protective paper** from the vial adapter. **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter, germs from your fingers can be transferred.
Step D		**Place the vial on a flat and solid surface.** **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not remove the vial adapter from the vial.**
Step E		Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter. **Do not lift the vial adapter from the vial** when removing the protective cap.
3. Attach the Plunger Rod and the Syringe		
Step F		Grasp the plunger rod by the wide top end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred. **Immediately** connect the plunger rod to the syringe by turning it clockwise into the plunger inside the prefilled syringe until resistance is felt.

Step G		**Remove the syringe cap** from the prefilled syringe by bending it down until the perforation breaks. **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred. **If the syringe cap is loose or missing, do not use the prefilled syringe.**
Step H		**Screw the prefilled syringe securely** onto the vial adapter until resistance is felt.
4. Reconstitute the Powder with the Solvent		
Step I		**Hold the prefilled syringe slightly tilted** with the vial pointing downwards. **Push the plunger rod** to inject all the solvent into the vial.
Step J		**Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** **Check the reconstituted solution.** It must be clear to slightly opalescent (slightly unclear). **If you notice visible particles or discoloration, do not use it.** Use a new package instead.

ZONOVATE® is recommended to be used immediately after it has been reconstituted. This is because if left, the medicine may no longer be sterile and could cause infections.

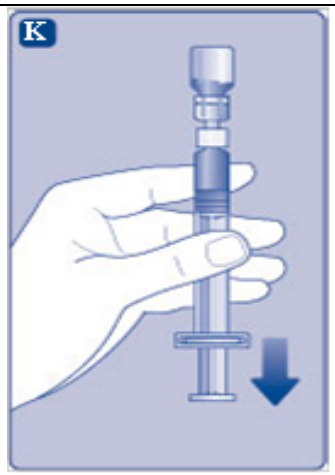
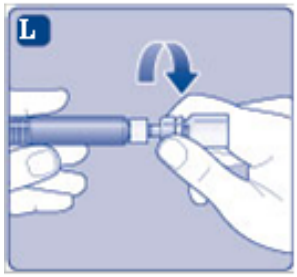
If you cannot use the reconstituted ZONOVATE® solution immediately, it must be used within 24 hours when stored in the refrigerator at 2°C - 8°C, within 4 hours when stored at room temperature up to 30°C, or within 2 hours when stored between 30°C and 40°C. Store the reconstituted product in the vial, with the vial adapter and the syringe still attached.

Do not freeze reconstituted ZONOVATE® solution or store it in syringes.

Do not store the solution without your doctor's advice.

Keep reconstituted ZONOVATE® solution out of direct light.

If your dose requires more than one vial, repeat step **A** to **J** with additional vials, vial adapters and prefilled syringes until you have reached your required dose.

Step K		**Keep the plunger rod pushed completely in.** **Turn the syringe** with the vial upside down. **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe. **Pull the plunger rod slightly downwards** to draw the reconstituted solution into the syringe. **In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.** If, at any point, there is too much air in the syringe, inject the air back into the vial. While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top. **Push the plunger rod** slowly until all air bubbles are gone.
Step L		**Unscrew the vial adapter** with the vial. **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.

5. Inject the Reconstituted Solution

ZONOVATE® is now ready to inject into your vein.

- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.
- Do not mix ZONOVATE® with any other intravenous infusions or medications.

Injecting ZONOVATE® via needleless connectors for intravenous (IV) catheters

Caution: The MixPro® prefilled solvent syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the prefilled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 mL plastic syringe for withdrawal of the reconstituted solution. This should be done right after step J.
- If the CVAD line needs to be flushed before or after ZONOVATE® injection, use 0.9% Sodium Chloride solution for injection.

If you have encountered any problems with attaching the prefilled solvent syringe to any luer-lock compatible device, or have any questions please contact Novo Nordisk at 1-800-465-4334.

6. Disposal

Step M		**After injection, safely dispose** of all unused ZONOVATE® solution, the syringe with the infusion set, the vial with the vial adapter, and other waste materials as instructed by your healthcare provider. Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.
Do not reuse the equipment.