PRODUCT MONOGRAPH

ZONOVATE®

Antihemophilic Factor (Recombinant, B-Domain Truncated)

Turoctocog alfa

Lyophilized Powder

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

Coagulation Factor VIII

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ZONOVATE®

Antihemophilic Factor (Recombinant, B-Domain Truncated)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	Lyophilized powder and solvent for solution for injection 250, 500, 1000, 1500, 2000 and 3000 IU/vial	Sodium chloride, sucrose *For a complete listing see Dosage Forms, Composition and Packaging section.*

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. The specific activity of **Zonovate®** is approximately 8300 IU/mg protein.

INDICATIONS AND CLINICAL USE

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.

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.

Pediatrics (<18 years of age):
The safety and efficacy of **Zonovate®** have been demonstrated in pediatric patients from 1 to <18 years old.

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 the Dosage Forms, Composition and Packaging section of the product monograph.

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.

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 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

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).

It is strongly recommended that every time that **Zonovate®** is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

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. Data on surgery were not available for children.

Special Populations

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.

Nursing Women: 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.

Pediatrics (<18 years of age):

Table 1-1: Pediatric Patients by Age Group

	0–<6 years	6–<12 years	12–<18 years	Total
Number of dosed patients	31	32	24	87
Number of patients on routine prophylaxis	31	32	24	87
Number of patients treated for breakthrough bleeds	24	25	21	71

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).

Geriatrics (>*65* years of age): Clinical studies of **Zonovate®** did not include patients above 65 to determine whether they respond differently from younger patients.

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 an inhibitor, 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions are defined as adverse events evaluated as possibly or probably related to **Zonovate®** by the investigator or Novo Nordisk.

During all clinical studies with **Zonovate®**, a total of 30 adverse reactions were reported in 19 of 214 patients exposed to **Zonovate®**. Of the 30 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to 18 years of age and 28 were reported in 18 of 127 adults. The most frequently reported adverse reactions were injection site reactions (2.3%) and hepatic enzymes increased (1.4%).

Immunogenicity

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

FVIII inhibitors: No patients developed inhibitors to Factor VIII. 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.

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).

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

Clinical Trial Adverse Drug Reactions

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

Table 1-2: Summary of Adverse Drug Reactions with a Frequency of ≥ 1% in Clinical Studies*

	Number of Patients	% of Patients with Adverse Reactions	Number of Adverse Reactions
Number of Patients	214		
General disorders and administration site conditions Injection site reactions**	5	2.3	5
Hepatobiliary disorder Hepatic enzymes increased***	3	1.4	4

* Calculated based on total number of unique patients in all clinical studies (214)
** Injection site reactions include: injection site erythema, injection site extravasation and injection site pruritus
*** Hepatic enzymes increased includes: alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and bilirubin

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

Cardiac disorders: Sinus tachycardia (0.5%)
General disorders and administration site conditions: Pyrexia (0.9%), fatigue (0.5%), feeling hot (0.5%), edema peripheral (0.5%)
Injury, poisoning and procedural complications: Contusion (0.5%)
Investigation: Heart rate increased (0.5%)
Musculoskeletal and connective tissue disorders: Arthropathy (0.9%), musculoskeletal pain (0.5%), musculoskeletal stiffness (0.5%), pain in extremity (0.5%)
Nervous System Disorder: Dizziness (0.5%), headache (0.5%)
Psychiatric disorders: Insomnia (0.5%)
Skin and subcutaneous tissue disorders: Rash (0.5%)
Vascular disorders: Hypertension (0.5%), lymphedema (0.5%)

DRUG INTERACTIONS

Drug interaction studies have not been performed with **Zonovate®**.

DOSAGE AND ADMINISTRATION

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 safety and efficacy in previously untreated patients have not yet been established.
- The number of units of Factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for Factor VIII products. The activity of Factor VIII in plasma is expressed either as 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.

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 1-3. 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 1-3.

Table 1-3: 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 1-4. 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 1-4.

Table 1-4: Dosing for Perioperative Management

Type of surgical procedure	Factor VIII level required (IU/dl or % or 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 1-5.

Table 1-5 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

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.

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

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

Administration

- **Zonovate®** is recommended to be used immediately after it has been reconstituted.
- If you cannot use the reconstituted **Zonovate®** solution immediately, it should be kept in the vial, with the vial adapter and the syringe still attached, at room temperature below 30°C for no longer than 4 hours, or refrigerated at 2°C - 8°C for no longer than 24 hours.
- 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.
- 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 PART III of the Product Monograph.

OVERDOSAGE

For management of a suspected drug overdose, contact your hemophilia treatment centre or your regional Poison Control Centre.

No symptoms associated with overdose were reported.

ACTION AND CLINICAL PHARMACOLOGY

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.

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.

Pharmacokinetics

All pharmacokinetic studies with **Zonovate®** were conducted in previously treated patients with severe hemophilia A (Factor VIII ≤ 1%). The analysis of plasma samples was conducted 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 1-6.

Table 1-6: 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/mL)/(IU/kg)	0.019 (0.004)	0.028 (0.006)
AUC (IU*h/mL)	13.64 (4.14)	18.70 (5.08)
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/mL)	1.02 (0.21)	1.54 (0.29)
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 1-7 for both groups.

Table 1-7: 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/mL)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.006)	0.025 (0.006)
AUC (IU*h/mL)	9.89 (4.14)	11.09 (3.73)	12.21 (4.38)	14.36 (3.48)
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/mL)	1.00 (0.58)	1.07 (0.35)	1.12 (0.31)	1.25 (0.27)
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 $t_{½}$ 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.

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

STORAGE AND STABILITY

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. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Record the beginning of storage at room temperature on the product carton.

Do not use **Zonovate®** after the end of the 12 month period at room temperature storage, 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 stored at 2°C – 8°C and 4 hours stored at ≤ 30°C. From a microbiological point of view, **Zonovate®** should be used immediately after reconstitution. If the reconstituted product is not used immediately, it should be used within 4 hours when stored at ≤ 30°C or within 24 hours when stored at 2°C - 8°C. Store the reconstituted product in the vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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 components:

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

Chemical name: Turoctocog alfa

Molecular formula: $C_{7480}H_{11379}N_{1999}O_{2194}S_{68}$

Molercular Mass: 166 kDa (calculated excluding post-translational modifications)

Structural formula:

Figure 1: Primary structure of Antihemophilic Factor (Recombinant, B-Domain Truncated) with disulfide bridges indicated

Physicochemical properties:

Appearance, colour, physical state	The purified turoctocog alfa is contained in a solution. The solution is clear and colourless
Solubility	The physical appearance of turoctocog alfa is a solution
Aqueous pH-solubility profile	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.
pI value	As turoctocog alfa is a mixture of different glycoforms, it does not possess a distinct pI value

Product Characteristics

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 2. Six potential tyrosine sulfation sites are present in the molecule and all have been confirmed. 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 2. An overview of the FVIII domains is provided below.

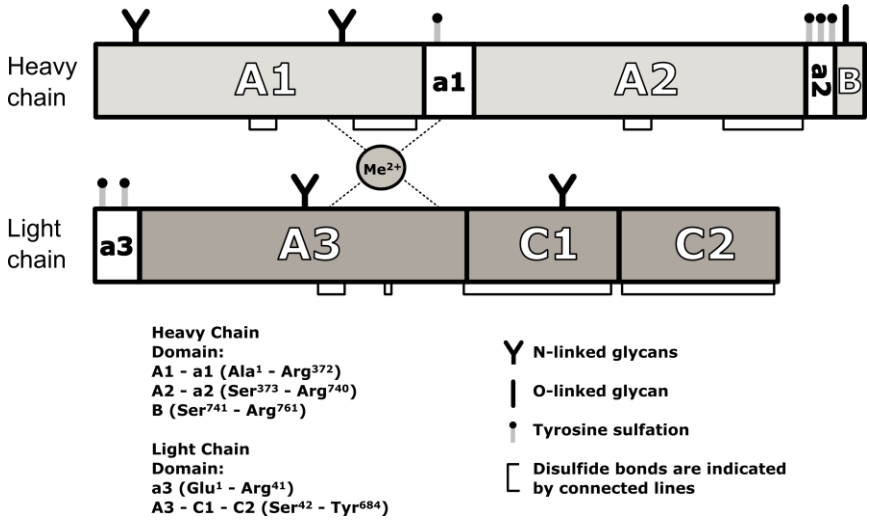

Figure 2: Antihemophilic Factor (Recombinant, B-Domain Truncated) structure showing FVIII domains (A1, a1, A2, a2, B, a3, A3, C1, C2) and post-translational modifications

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.

CLINICAL TRIALS

Study demographics and trial design

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 on safety and efficacy of **Zonovate®** in prevention and treatment of bleeds in previously treated patients with hemophilia A. Sub-Trial: Safety and efficacy of **Zonovate®** in prevention and treatment of bleeding during surgical procedures in patients with hemophilia A.	*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.	Total trial (including sub-trial): 150 adolescent or adult patients with severe hemophilia A. Surgery sub-trial: 9 adolescent or adult patients with severe hemophilia A	Mean = 28 years Range = 12 to 60 years	Male
Trial 3545 (Pediatric Trial)	A multi-centre, open-label, non-controlled trial on safety and efficacy of **Zonovate®** in previously treated pediatric patients with hemophilia A.	*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 pediatric patients (below 12 years of age) with severe hemophilia A	Mean = 6 years Range = 1 to 11 years	Male
Trial 3568 (Extension Trial of 3543 and 3545)	Safety and efficacy of **Zonovate®** in prevention and on-demand treatment of bleeding episodes in patients with hemophilia A Sub-trial: Efficacy and safety of **Zonovate®** in prevention and treatment of bleeding during surgical procedures in patients with hemophilia A	*Preventive* 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 *Surgery* At the investigator's discretion. Target FVIII trough activity >0.5 IU/mL. Doses according to local standard practice at the treatment centre	55 pediatric, 23 adolescent and 110 adult patients with severe hemophilia A	Mean = 21 years Range = 1 to 60 years	Male

* At inclusion in the trial**.**

Study results

Three multi-centre, open-label, non-controlled trials have been conducted to evaluate the safety and efficacy of **Zonovate®** in the prevention and treatment of bleeds in previously treated patients with severe hemophilia A (Factor VIII activity ≤1%). These include one pivotal trial in 150 adults and adolescents (study 3543), one study in 63 pediatric patients (study 3545) and one extension trial (study 3568).

The studies included 213 exposed patients: 24 adolescents between 12 and 18 years, 126 adult patients between 18 and 60 years old (≥150 exposure days) participated in the pivotal trial and 63 pediatric patients (31 aged 1 to < 6 and 32 aged 6 to < 12) (≥50 exposure days) without inhibitors participated in the pediatric trial. 187 out of 213 patients continued in the safety extension trial. All subjects received preventive treatment. Breakthrough bleeding episodes in patients treated for routine prophylaxis and in 14 patients who underwent surgery (14-54 years) were treated at the investigator's discretion.

During an accumulated exposure of more than 54,000 days (corresponding to 342 patient years), no Factor VIII inhibitor development was observed in the phase 3a clinical trials.

Routine Prophylaxis

213 subjects received **Zonovate®** for routine prophylaxis. The prophylactic regimen for the 150 adolescent and adult subjects consisted of 20-40 IU/kg every other day or 20-50 IU/kg three times per week. The prophylactic regimen for the 63 pediatric subjects consisted of 25-50 IU/kg every other day or 25-60 IU/kg three times per week. The majority of the subjects (>80%) were treated with the three times per week regimen.

Table 2-1: Annualized Bleeding Rate (ABR) and Dose Used for 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	126	213
Trial 3543 (Adults & Adolescents)					
Number of patients	-	-	24	126	150
Mean ABR *			5.6	6.7	6.5
Median ABR (IQR)			4.0 (6.8)	3.6 (9.0)	3.7 (8.7)
Dose used for prevention per patient (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*	4.7	5.9			5.3
Median ABR (IQR)	3.0 (6.1)	3.6 (8.7)			3.0 (8.5)
Dose used for prevention per patient (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	109	187
Mean ABR*	2.3	2.8	2.8	3.4	3.1
Median ABR (IQR)	1.4 (3.0)	1.4 (4.3)	1.6 (3.3)	1.9 (3.6)	1.7 (3.6)
Dose used for prevention per patient (IU/kg BW)					
Mean (SD)	42.1 (9.9)	38.1 (9.1)	29.5 (9.4)	29.0 (7.9)	31.5 (9.7)
Min ; Max	3.9 ; 82.7	20.3 ; 71.4	20.0 ; 73.9	12.0 ; 86.0	3.9 ; 86.0

BW: Body weight, SD: Standard deviation. IQR: Interquartile range.
*Mean estimated from a Poisson model allowing for over-dispersion .
**Success defined as either 'Excellent' or 'Good'.

Control of Breakthrough Bleeding Episodes

A total of 499 bleeds in adolescents and adults (study 3543) and 126 bleeds in pediatric patients (study 3545) was reported. An additional 752 bleeds were reported in the extension (study 3568, including all age groups). 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, the treatment was considered a failure. 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, 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, 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 study, bleeds were classified as mild/moderate in 88% of the cases and as severe in 12% of the cases. The majority of the bleeds (59%) were spontaneous and 41% were caused by trauma. Joints were the most frequent locations of bleeds, accounting for 72%.

Table 2-2: Consumption of Zonovate® and Hemostatic Efficacy by Age Group and Study

	Younger children (0−<6 years)	Older children (6−<12 years)	Adolescents (12−<18 years)	Adults (≥18 years)	Total
Study 3543 (Adults & Adolescents)					
Number of patients	-	-	24	126	150
Number of bleeds	-	-	67	432	499
Dose used for treatment of bleed (IU/kg BW) Mean (SD) Min ; Max	-	-	24.7 (8.7) 12.4 ; 48.4	31.4 (10.9) 9.8 ; 61.1	30.4 (10.8) 9.8 ; 61.1
Success rate* %	-	-	71.6%	82.2%	80.8%
% of bleeds stopped by one or two infusions	-	-	89.6%	89.4%	89.4
Study 3545 (Pediatrics)					
Number of patients	31	32	-	-	63
Number of bleeds	53	73	-	-	126
Dose used for treatment of bleed (IU/kg BW) Mean (SD) Min ; Max	45.5 (23.7) 25.9 ; 193.8	37.6 (10.2) 25.5 ; 63.6	-	-	40.4 (16.6) 25.5 ; 193.8
Success rate* %	96.2%	89.0%	-	-	92.1%
% of bleeds stopped by one or two infusions	98.1%	93.2%	-	-	95.2%
Study 3568 (Extension Study)					
Number of patients	27	28	23	109	187
Number of bleeds	59	80	81	532	752
Dose used for treatment of bleed (IU/kg BW) Mean (SD) Min ; Max	43.5 (10.4) 26.3 ; 67.4	42.4 (10.2) 28.2 ; 65.5	31.1 (10.5) 18.1 ; 76.8	35.7 (12.2) 9.3 ; 104.0	36.2 (12.2) 9.3 ; 104.0
Success rate* %	89.8%	88.8%	86.4%	88.3%	88.3%
% of bleeds stopped by one or two infusions	98.3%	88.8%	84.0%	90.4%	90.2%

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

Table 2-3: Success Rate for Hemostatic Response by Site of Bleed, by Age Group and by Study

Site of bleed	Total Bleeds (success rate)	Younger children (0−<6 years) Bleeds (success rate)	Older children (6−<12 years) Bleeds (success rate)	Adolescents (12−<18 years) Bleeds (success rate)	Adults (≥18 years) Bleeds (success rate)
Study 3543 (Adults & Adolescents)					
Joint	389 (80.2%)	-	-	52 (71.2%)	337 (81.6%)
Subcutaneous	13 (69.2%)	-	-	6 (66.7%)	7 (71.4%)
Muscular	26 (88.5%)	-	-	6 (66.7%)	20 (95.0%)
Gastro-intestinal	3 (66.7%)	-	-	0 (-)	3 (66.7%)
Other[b]	46 (82.6%)	-	-	3 (100%)	43 (81.4%)
Missing[c]	22 (86.4%)	-	-	0 (-)	22 (86.4%)
Study 3545 (Pediatrics)					
Joint	59 (96.6%)	24 (95.8%)	35 (97.1%)	-	-
Subcutaneous	15 (100%)	7 (100%)	8 (100%)	-	-
Muscular	13 (100%)	6 (100%)	7 (100%)	-	-
Mucosal	7 (85.7%)	6 (83.3)	1 (100%)	-	-
Other[b]	30 (83.3%)	10 (100%)	20 (75.0%)	-	-
Missing[c]	2 (-)	-	2 (-)	-	-
Study 3568 (Extension Study)					
Joint	586 (88.4%)	25 (84.0%)	51 (84.3%)	67 (88.1%)	443 (89.2%)
Subcutaneous	38 (89.5%)	13 (92.3%)	9 (100%)	2(50.0%)	14 (85.7%)
Muscular	49 (81.6%)	4 (100%)	7 (85.7%)	4(75.0%)	34 (79.4%)
Gastro-intestinal	2 (50.0%)	1 (0%)	0(-)	0 (-)	1 (100%)
Mucosal	17 (88.2%)	7 (100%)	2(100%)	0 (-)	8 (75.0%)
Other[b]	57 (93.0%)	9 (100%)	9(100%)	8(87.5%)	31 (90.3%)
Missing[c]	3 (100.0%)	0 (-)	2 (100%)	0 (-)	1 (100%)

[a] Success rate: Number of 'Excellent' or 'Good' hemostatic responses/number of bleeds

[b] Other: The location was reported as "other" in the diary. This field was used to report bleeds for which there was no other obvious pre-specified location. 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

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 14 surgeries were performed in 14 patients. Apart from 1 adolescent, all the patients undergoing surgery were adults. Hemostasis was successful in all surgeries and no treatment failures were reported.

Table 2-4: Hemostatic Response by Surgical Procedure in the Pivotal Trial and Extension Trial

Description of surgery	Type	Hemostatic response [a]	Patient age (years)
Study 3543 (Adults & Adolescents)			
Left knee replacement	Major	Excellent	36
Arthroscopy and synovectomy, partial menisectomy	Minor	Good	30
Surgical extraction of tooth 48 and radix of tooth 12	Minor	Excellent	22
Right knee synovectomy with extirpation of ostheosynthetic graft	Major	Good	25
Circumcision	Minor	Excellent	14
Left total hip arthroplasty	Major	Excellent	25
Right ankle synovectomy	Major	Excellent	29
Right ankle synovectomy	Major	Excellent	24
Right ankle synovectomy	Major	Excellent	18
Study 3568 (Extension Study)			
Arthroscopy of left ankle	Major	Excellent	24
Left hip arthroprosthesis, reduction finger fracture	Major	Good	55
Panprotocolectomy; Ileo-anal Pouch	Major	Excellent	21
Right knee arthro-prosthesis	Major	Good	28
Knee replacement and elbow radial head excision	Major	Good	41

[a] Hemostatic response during surgery

DETAILED PHARMACOLOGY

Factor VIII is essential for blood coagulation and hemophilia A patients lacking Factor VIII suffer from recurrent bleeding episodes. Thrombin-activated Factor VIII (FVIIIa) functions as cofactor for factor IXa (FIXa) on the surface of activated platelets where the FVIIIa/FIXa complex converts factor X to activated factor X (FXa). Factor VIII is a large, complex glycoprotein that is synthesized in the liver and Factor VIII circulates in a non-covalently bound complex with von Willebrand Factor (vWF). The complex with vWF protects Factor VIII from binding to clearance receptors and phospholipid surfaces. The plasma half-life of Factor VIII in complex with vWF is approximately 12 hours in humans.

The stability of Factor VIII in circulation relies on its tight non-covalent interaction with its carrier protein vWF. Without the protection that binding of Factor VIII to vWF offers, the clearance of Factor VIII is increased dramatically as can be observed in patients lacking vWF (type 3 vWF disease), leading to a deficiency of endogenous Factor VIII and resulting in a strongly reduced half-life of i.v. administered Factor VIII. The interaction with vWF was studied and confirmed in *in vitro* pharmacology studies in which **Zonovate®** was found to bind with similar binding affinities as Factor VIII to vWF.

Non-clinical Pharmacology

No safety concerns were identified in safety pharmacology investigations performed in Cynomolgus monkeys, as there were no effects on any of the safety pharmacology parameters, e.g. no effects on respiratory rate or depth, no effect on behavioural, autonomic or neurological measurements and no effect of treatment on heart rate, ECG intervals or waveform and the no observed adverse effect level (NOAEL) was 5000 IU/kg, the highest dose tested.

Clinical Pharmacology

In vitro studies were performed with normal and Factor VIII-deficient human blood or plasma. The studies demonstrated that the primary pharmacodynamic properties of **Zonovate®** are consistent with those described in the literature for endogenous Factor VIII, as an important co-factor in the activation of coagulation factor X (FX) in the human coagulation cascade leading to thrombin generation and the formation of a stable fibrin clot.

Clinical Pharmacokinetics

Refer to ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics.

TOXICOLOGY

Carcinogenicity, Genotoxicity, Reproductive Toxicity

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

An overview of the non-clinical toxicity studies is listed in Table 2-5.

Table 2-5: Overview of 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.
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, neutralising-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

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PART III: CONSUMER INFORMATION

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

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

ABOUT THIS MEDICATION

What the medication is used for:
Zonovate® is used to treat and prevent bleeding episodes in patients with hemophilia A.

What it does:
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.

When it should not be used:
Do not use **Zonovate®** unless your doctor confirms that you have hemophilia A.

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.

What the medicinal ingredient is:
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.

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.

What the non-medicinal ingredients are:
Zonovate® contains the following non-medicinal ingredients: calcium chloride dihydrate, L-histidine, L-methionine, polysorbate 80, sodium chloride, sucrose.

What dosage forms it comes in:
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.

WARNINGS AND PRECAUTIONS

BEFORE you use **Zonovate®** talk to your doctor or pharmacist if:

- You are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or

herbal medicines.
- You are pregnant or breast-feeding, or if you think that you may be pregnant or are planning to have a baby.

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 section "SIDE EFFECTS AND WHAT TO DO ABOUT THEM".

INTERACTIONS WITH THIS MEDICATION

There are no known interactions of **Zonovate®** with other medicinal products.

PROPER USE OF THIS MEDICATION

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. 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.

Data on the use of **Zonovate®** during surgeries in children are not available.

Overdose:
If you use more **Zonovate®** than you should, tell your doctor, your hemophilia treatment centre or go to a hospital immediately.

In case of drug overdose, contact a health care practitioner, 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 your 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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.

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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Lack of effect (bleeding does not stop after taking **Zonovate®**)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
Uncommon	Allergic reactions (such as 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)			✓

This is not a complete list of side effects. For any unexpected effects while taking **Zonovate®**, *contact your doctor or pharmacist.*

Reporting Side Effects

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

3 ways to report:

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

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

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

HOW TO STORE IT

Keep 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.

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, or at room temperature (below 30°C) for a single period not exceeding 12 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 from this date or 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 **Zonovate®** solution immediately, it can be kept in the vial, with the vial adapter and the syringe still attached, at room temperature (below 30°C) for no longer than 4 hours or in the refrigerator at 2°C – 8°C for no longer than 24 hours. 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.

MORE INFORMATION

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

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

This leaflet was prepared by Novo Nordisk Canada Inc.

Last revised: May 2017

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.

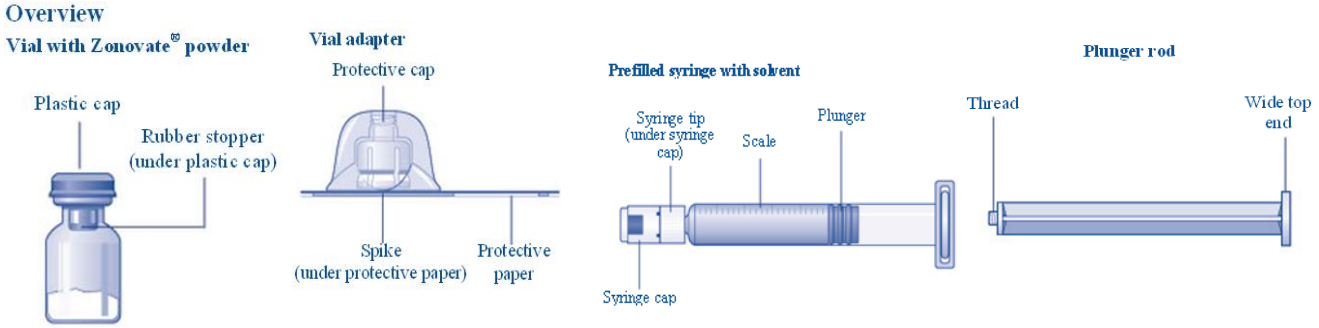
Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

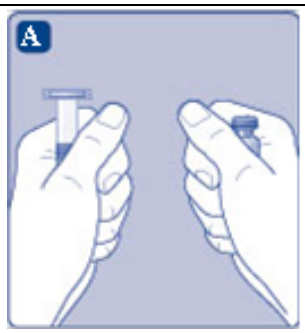
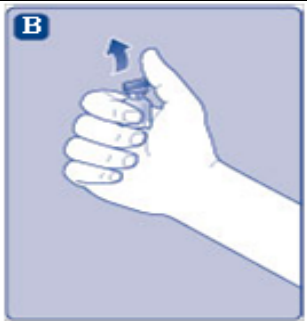
Contents

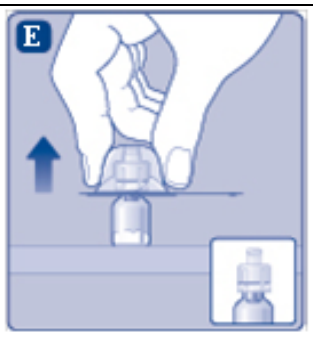
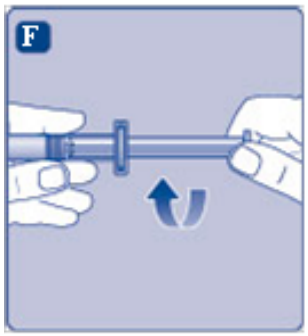
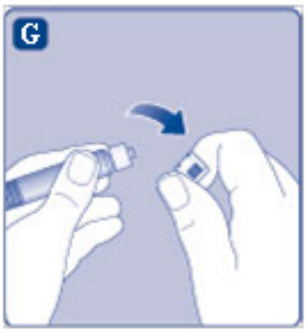
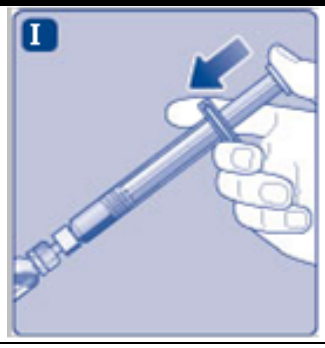
The package contains:
- 1 vial with **Zonovate®** powder
- 1 vial adapter
- 1 prefilled syringe with solvent
- 1 plunger rod (placed under the syringe)

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



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.

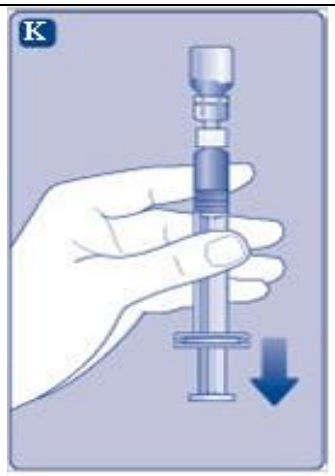
If you cannot use the reconstituted Zonovate® solution immediately, it should be kept in the vial, with the vial adapter and the syringe still attached, at room temperature (below 30°C) for no longer than 4 hours or in the refrigerator at 2°C–8°C for no longer than 24 hours.

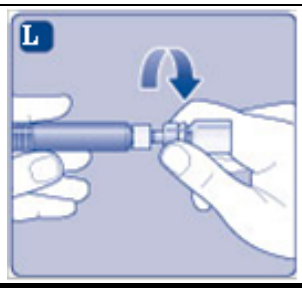
Do not freeze reconstituted Zonovate® solution or store it in syringes.

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.