P&T Summary

Indications and Usage

ESPEROCT® [antihemophilic factor (recombinant), glycopegylated-exei] is indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes

- ESPEROCT® is not indicated for the treatment of von Willebrand disease

Selected Important Safety Information

Contraindications

- Do not use in patients who have known hypersensitivity to Esperoct® or its components, including hamster proteins

Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis, may occur. Should hypersensitivity reactions occur, discontinue ESPEROCT® and administer appropriate treatment

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Please see additional Important Safety Information on page 34.
Please click here for Prescribing Information.

esperoct®
antihemophilic factor (recombinant), glycopegylated-exei

Table of Contents

Section IA: Background on Hemophilia

Disease State Overview

The process of blood coagulation is designed to restore hemostasis after damage to a blood vessel. The blood coagulation system involves multiple cell types and specialized proteins (enzymes and their cofactors) and is highly regulated.[1] Dysfunction of blood coagulation can result in prolonged bleeding with life-threatening and potentially fatal consequences.[2,3]

Congenital hemophilia is one of many bleeding disorders caused by malfunction of the coagulation system. It is characterized by improper clot formation that leads to prolonged bleeding.[2] There are two main subtypes of congenital hemophilia A and B, which are differentiated by deficiency of blood coagulation factors VIII and IX, respectively.[3] Congenital hemophilia is classified as mild, moderate, or severe based on endogenous plasma factor VIII and IX levels of >5%, 5% to 1%, and <1%, respectively.[3]

Most patients are diagnosed at an early age; the median age of hemophilia diagnosis is 36 months with mild disease, 8 months with moderate disease, and 1 month with severe disease. Symptoms of congenital hemophilia A and B can be indistinguishable and include increased bruising, bleeding into muscles and joints, spontaneous bleeding with unknown cause, and prolonged bleeding following trauma.[3]

Pathophysiology of Congenital Hemophilia A

Coagulation is a highly regulated process initiated upon vessel wall injury. Substances released by the injured vessel interact with circulating coagulation factors to activate platelets that go to the site of injury. These activated platelets adhere to the injured site and serve as a scaffold for building a stable blood clot.[4,5]

Factor VIII is an essential coagulation protein involved in clot formation.[1,5] When activated, factor VIII serves as a cofactor for activated factor IX (FIXa), which then activates factor X. Activated factor X interacts with other coagulation proteins, leading to a thrombin burst and clot formation.[1,4,5]

Congenital hemophilia A is an X-linked inherited disorder characterized by a deficiency or an abnormality in coagulation FVIII caused by mutations in the FVIII gene, *F8*.[3] This deficiency of coagulation factor VIII results in decreased thrombin generation and clot formation.[5] Although a majority of patients with hemophilia inherit the disorder, about one-third of cases result from a spontaneous mutation and have no known family history.[3,6]

Epidemiology of Congenital Hemophilia A

Congenital hemophilia A is more common than congenital hemophilia B, representing ~80% to 85% of the hemophilia population.[3] Approximately ~31,600 people in the United States have hemophilia and ~23,900 of those have hemophilia A.[7] Congenital hemophilia A occurs at an incidence of 1 in 5000 to 7000 male births.[8] Hemophilia affects mostly males, and its prevalence is similar across different racial groups.[3,9]

Burden of Disease

Bleeding into muscle tissue and joints causes swelling, stiffness, and pain, while bleeding into sites such as the head, throat, or gastrointestinal tract can be life-threatening.[3] Further, the physical symptoms of hemophilia, such as the tendency for repeat bleeding into target joints, can result in tissue damage, physical deformity, and subsequent loss of range of motion along with disability and chronic pain.[8,10] Studies have shown that hemophilia has a significant negative impact on a person's well-being. US data from The Hemophilia Utilization Group Study – Part Va (HUGS-Va) demonstrated that as the severity of hemophilia increased, overall physical abilities were significantly negatively impacted.[11]

Advances in hemophilia management in recent decades have led to a near normal life expectancy in patients with hemophilia.[11,12] However, hemophilia still leads to a greater risk of complications later in life, as well as age-related comorbidities.[11] In one study conducted between 1998 and 2011, 32% of hemophilia-related deaths were related to liver disease; HIV-related causes accounted for another 18.5% of deaths in this time period.[13]

Congenital hemophilia additionally poses a substantial economic burden for patients, the health care system, and society, as evidenced by many direct medical costs such as hospitalization, outpatient visits, laboratory tests, and drug costs.[14]

Treatment Options for Congenital Hemophilia A

Factor replacement therapies are the treatment of choice for people with hemophilia as they are safe and effective for treating and preventing bleeds.[3] Additionally, alternative treatment options are available, including a bispecific antibody mimicking factor VIII that can be used to treat bleeds prophylactically in people with hemophilia A.[15] Factor administration can be episodic in response to bleeding (on demand) or prophylactic to prevent bleeding.[9] Prophylaxis to prevent joint bleeding is especially important for individuals with severe disease.[3]

Various forms of factor VIII concentrates are available, including plasma-derived products and recombinant products.[10] Recombinant factor VIII products are the recommended treatment of choice for hemophilia A by the National Bleeding Disorders Foundation's Medical and Scientific Advisory Council (NBDF MASAC).[16]

Section IB: Product Introduction

ESPEROCT®: An Extended Half-life Recombinant Factor VIII Treatment

ESPEROCT® is a recombinant, B-domain truncated, extended half-life, factor VIII indicated for treatment of adults and children with hemophilia A. ESPEROCT® is PEGylated to delay degradation and thereby prolong its half-life. Purification of ESPEROCT® is accomplished through several chromatographic steps, including affinity chromatography, and two viral clearance steps (detergent treatment and filtration through a 20-nm pore).[17]

Vials of ESPEROCT® in lyophilized powder form can be stored for no longer than 12 months at room temperature up to 86°F (30°C) or up to 104°F (40°C) for no longer than 3 months. Please see Prescribing Information for complete storage instructions.[17]

Factor VIII inhibitors, antibodies produced by patients that bind and inhibit factor VIII activity, are the most significant treatment complication in individuals with hemophilia A, leading to increased morbidity and treatment costs.[18] In clinical trials of ESPEROCT® in previously treated patients (PTPs) (N=270), one subject developed confirmed inhibitors to factor VIII. In a clinical trial of ESPEROCT® in previously untreated patients (PUPs) <6 years of age, of the 80 treated subjects, 21 (26.3%) subjects developed Factor VIII inhibitors (≥0.6 Bethesda Units).[17]

Section II: Review of Prescribing Information for ESPEROCT®[17]

1 INDICATIONS AND USAGE

ESPEROCT® [antihemophilic factor (recombinant), glycopegylated-exei] is a recombinant DNA-derived coagulation Factor VIII concentrate indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitation of Use:

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

2 DOSAGE AND ADMINISTRATION

For intravenous infusion after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of the Factor VIII deficiency, on the location and extent of bleeding, and on the patient's clinical condition. Careful monitoring of replacement therapy is necessary in cases of major surgery or life-threatening bleeding episodes.
- Each vial of ESPEROCT® contains the labeled amount of recombinant Factor VIII in international units (IU). One IU of Factor VIII activity corresponds to the quantity of Factor VIII in one milliliter of normal human plasma. The calculation of the required dosage of Factor VIII is based on the empirical finding that one IU of Factor VIII per kg body weight raises the plasma Factor VIII activity by two IU/dL.

2.1 Dose (cont'd)

On-demand Treatment and Control of Bleeding Episodes

Table 1 can be used to guide dosing of ESPEROCT® for treatment of bleeding episodes.

Table 1: Dosing of ESPEROCT® to Control Bleeding Episodes

Type of bleeding	Adolescents/Adults ≥12 years Dose (IU/kg)	Children <12 years Dose (IU/kg)	Additional doses
Minor Early hemarthrosis, mild muscle bleeding, or oral bleeding	40	65	One dose should be sufficient
Moderate More extensive hemarthrosis, muscle bleeding, or hematoma	40	65	An additional dose may be administered after 24 hours
Major Life- or limb-threatening hemorrhages, gastrointestinal bleeding, intracranial, intra-abdominal or intrathoracic bleeding, fractures	50	65	Additional dose(s) may be administered approximately every 24 hours

2.1 Dose (cont'd)

Perioperative Management

The dose level and dosing intervals for surgery depend on the procedure and local practice. A guide for dosing with ESPEROCT® during surgery (perioperative management) is provided in **Table 2** below.

Table 2: Dosing for Perioperative Management with ESPEROCT®

Type of surgery	Adolescents/Adults ≥12 years Pre-operative Dose (IU/kg)	Children <12 years Pre-operative Dose (IU/kg)	Additional doses
Minor Including tooth extraction	50	65	Additional dose(s) can be administered after 24 hours if necessary
Major Intracranial, intra-abdominal, intrathoracic, or joint replacement surgery	50	65	Additional doses can be administered approximately every 24 hours for the first week and then approximately every 48 hours until wound healing has occurred

Routine Prophylaxis

Adults and adolescents (≥12 years): The recommended starting dose is 50 IU of ESPEROCT® per kg body weight every 4 days. This regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.

Children (<12 years): A dose of 65 IU of ESPEROCT® per kg body weight twice weekly. This regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.

- ESPEROCT® also may be dosed to achieve a specific target Factor VIII activity level, depending on the severity of hemophilia, for on-demand treatment/control of bleeding episodes or perioperative management. To achieve a specific target Factor VIII activity level, use the following formula:

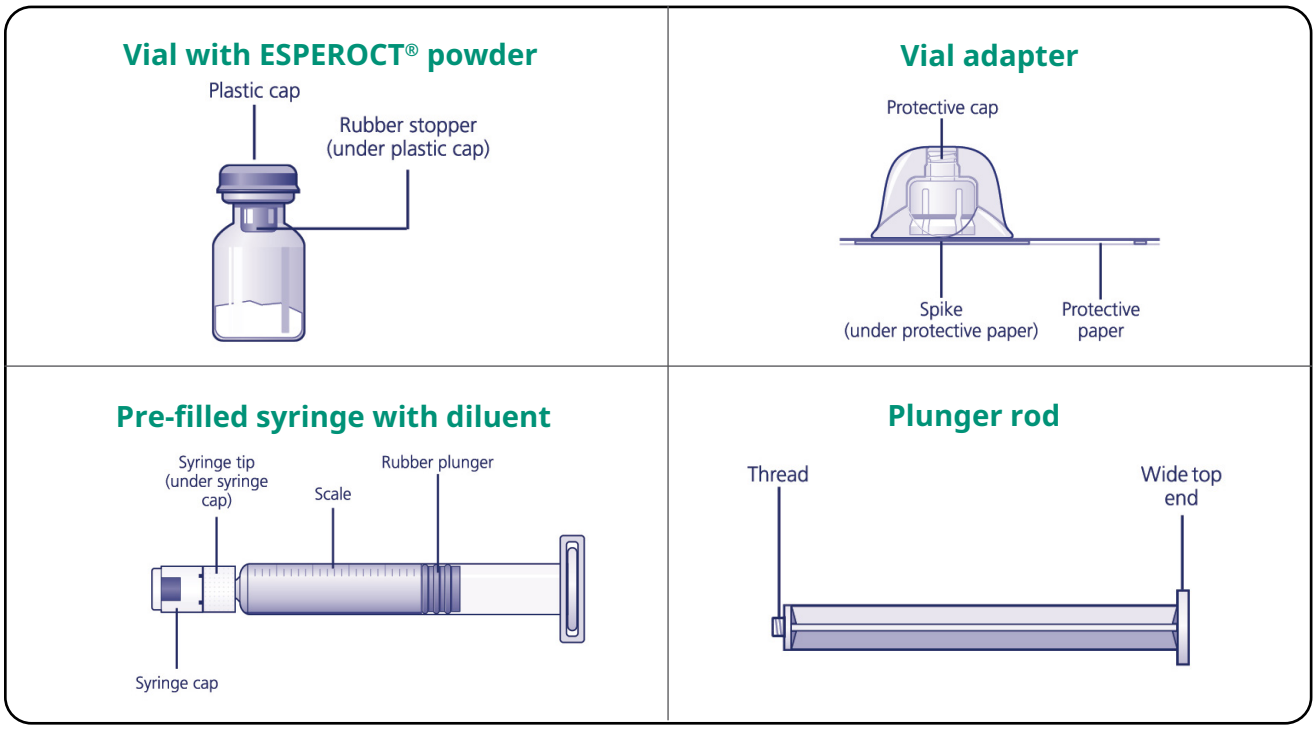
Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5

- Base the dose and frequency of ESPEROCT® on the individual clinical response. Patients may vary in their pharmacokinetic and clinical responses.
- If monitoring of Factor VIII activity is performed, use a chromogenic or one-stage clotting assay appropriate for use with ESPEROCT® [*see Warnings and Precautions (5.3)*].

2.2 Preparation and Reconstitution

- Always wash hands and ensure that the area is clean before performing the reconstitution procedures.
- Use aseptic technique during the reconstitution procedures.
- If the dose requires more than one vial of ESPEROCT® per infusion, reconstitute each vial according to the following instructions.

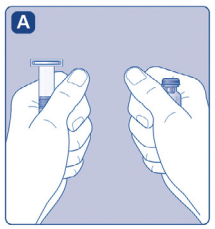
Overview of ESPEROCT® Package



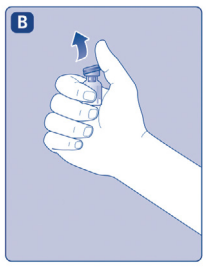
2.2 Preparation and Reconstitution (cont'd)

Reconstitution

1. Bring the ESPEROCT® vial and the pre-filled diluent syringe to room temperature.

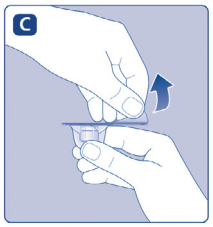


2. Remove the plastic cap from the ESPEROCT® vial.

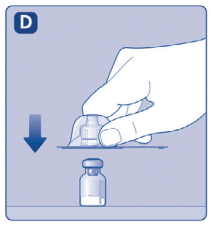


3. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry prior to use.

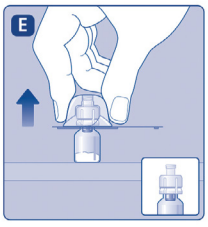
4. Remove the protective paper from the vial adapter. **Do not remove the vial adapter from the protective cap.**



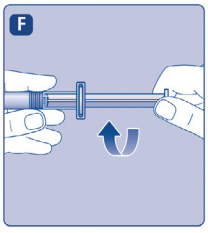
5. Place the ESPEROCT® vial on a flat and solid surface. While holding the protective cap, place the vial adapter over the ESPEROCT® vial and press down firmly on the protective cap until the vial adapter spike penetrates the rubber stopper.



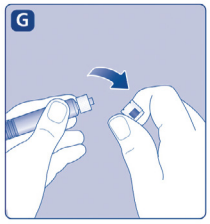
6. Carefully remove the protective cap from the vial adapter.



7. Grasp the plunger rod as shown in the diagram. Attach the plunger rod to the syringe by holding the plunger rod by the wide top end. Turn the plunger rod clockwise into the rubber plunger inside the pre-filled diluent syringe until resistance is felt.



8. Break off the syringe cap from the pre-filled diluent syringe by snapping the perforation of the cap.



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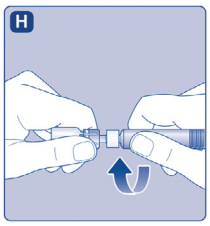
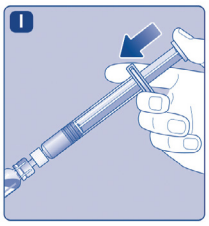
2.2 Preparation and Reconstitution (cont'd)

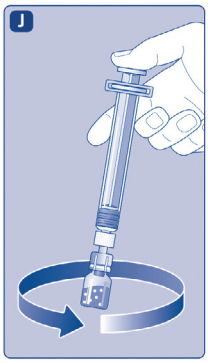
9. Connect the pre-filled diluent syringe to the vial adapter by turning it clockwise until it is secured.



10. Push the plunger rod to slowly inject all the diluent into the vial.



11. Without removing the syringe, gently swirl the ESPEROCT® vial until all of the powder is dissolved. Avoid shaking the vial and foaming the solution.



2.3 Administration

For intravenous infusion only.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and have no particles. Do not use if particulate matter or discoloration is observed.
- Do not administer ESPEROCT® in the same tubing or container with other medicinal products.
- Administer the ESPEROCT® solution immediately. If not, store the solution in the vial with the vial adapter and the syringe attached. Use ESPEROCT® within 4 hours when stored at ≤86°F (30°C) or within 24 hours when stored in a refrigerator at 36°F to 46°F (2°C to 8°C).

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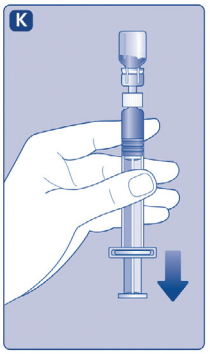
antihemophilic factor (recombinant), glycopegylated-exei

2.3 Administration (cont'd)



1. Invert the ESPEROCT® vial and slowly draw the solution into the syringe.
2. Detach the syringe from the vial adapter by turning the syringe counterclockwise.
3. Attach the syringe to the luer end of an infusion needle set.
4. Infuse the reconstituted ESPEROCT® intravenously slowly over approximately 2 minutes.
5. After infusion, safely dispose of the syringe with the infusion set, the vial with the vial adapter, any unused ESPEROCT®, and other waste materials.

Caution: The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches and is compatible with a standard Luer-lock connector.

Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®/MicroClave®, InVision-Plus®, InVision-Plus CS®, Invision-Plus Junior®, Bionector®), and their use can damage the connector and affect administration. To administer ESPEROCT® through incompatible needleless connectors, withdraw the reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.

3 DOSAGE FORMS AND STRENGTHS

ESPEROCT® is available as a sterile white to off-white lyophilized powder supplied in single-dose vials containing nominally 500, 1000, 1500, 2000, or 3000 IU. The actual FVIII activity is printed on each ESPEROCT® vial and carton.

After reconstitution with 4 mL of saline diluent, the reconstituted solution contains approximately 125, 250, 375, 500 or 750 IU per mL of ESPEROCT®, respectively.

4 CONTRAINDICATIONS

ESPEROCT® is contraindicated in patients who have known hypersensitivity to ESPEROCT® or its components (including hamster proteins) [*see Warnings and Precautions (5.1) and Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with ESPEROCT®. The product contains traces of hamster proteins, which in some patients may cause allergic reactions [*see Description (11)*]. Early signs of allergic reactions, which can progress to anaphylaxis, may include angioedema, chest tightness, difficulty breathing, wheezing, rash, hives, and itching. Observe patients for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of exposure to the product. Discontinue use of ESPEROCT® if allergic- or anaphylactic-type reactions occur, and initiate appropriate treatment.

5.2 Neutralizing Antibodies

The formation of neutralizing antibodies (inhibitors) to Factor VIII has occurred following administration of ESPEROCT®. Monitor patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If expected Factor VIII activity plasma levels are not attained, or if bleeding is not controlled after ESPEROCT® administration, suspect the presence of an inhibitor (neutralizing antibody) [*see Warnings and Precautions (5.3)*].

5.3 Decreased Incremental Recovery in Previously Untreated Patients

Incremental recovery (IR) is defined as the increase in plasma Factor VIII activity per IU/kg of ESPEROCT®. Decreased IR, defined as having at least 2 consecutive observations of low IR values (<0.6 (IU/dL)/(IU/kg)) after treatment with ESPEROCT®, was observed in a trial of PUPs <6 years of age within the first 5 exposure days (ED) to ESPEROCT®. Decreased IR was observed in 17 out of 59 (28.8%) subjects without factor VIII inhibition. This may be associated with high titers of anti-PEG binding antibodies. Decreased IR was temporary and returned to ≥ 0.6 (IU/dL)/(IU/kg) between 15 to 70 EDs if ESPEROCT® was continued.

As part of a post hoc subgroup analysis, the bleeding tendency was evaluated in the 17 subjects who experienced a temporary decreased IR. The mean treatment duration was 0.48 years, after which IR normalized in subjects continuing treatment (N=13). During the period of decreased IR, 14 out of 17 subjects experienced a total of 30 bleeds while on prophylaxis, of which 7 (23.3%) were spontaneous. For non-inhibitor, non-decreased IR subjects, 36 (18.1%) of the total 199 bleeding episodes (mean treatment duration of 3.71 years) were reported as spontaneous. Subjects with decreased IR may have an increased bleeding tendency during the decreased IR period [*see Adverse Reactions (6.2*)].

If bleeding is not controlled with the recommended dose of ESPEROCT® and/or the expected Factor VIII activity levels in the plasma are not attained and Factor VIII inhibitors are not detected, consider adjusting the dose, dosing frequency or discontinuing the product.

5.4 Monitoring Laboratory Tests

If monitoring of Factor VIII is performed, use a chromogenic or one-stage clotting assay appropriate for use with ESPEROCT® [*see Dosage and Administration (2)*].

Factor VIII activity levels can be affected by the type of activated partial thromboplastin time (aPTT) reagent used in the assay. Some silica-based aPTT reagents can underestimate the activity of ESPEROCT® by up to 60%; other reagents may overestimate the activity by 20%. If an appropriate one-stage clotting or chromogenic assay is not available locally, then use a reference laboratory.

If bleeding is not controlled with the recommended dose of ESPEROCT® or if the expected Factor VIII activity levels in plasma are not attained, then perform a Bethesda assay to determine if Factor VIII inhibitors are present.

6 ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥1%) in previously treated patients (PTPs) and previously untreated patients (PUPs) in clinical trials were rash, redness, itching (pruritus), and injection site reactions. Additional frequently reported adverse reactions (incidence ≥1%) in PUPs included Factor VIII inhibition (30%), and drug hypersensitivity (2.5%).

6.1 Clinical Trials Experience

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

The safety of ESPEROCT® has been evaluated in 270 subjects (202 adolescents/adults and 68 children) in five prospective, multi-center clinical studies in previously treated patients (PTPs) and 81 subjects (< 6 years of age) in one open-label, multi-center clinical study in previously untreated patients (PUPs) with severe hemophilia A (<1% endogenous Factor VIII activity) and no history of inhibitors. All subjects received at least one dose of ESPEROCT®. A previously treated patient was defined as a subject with a history of at least 150 exposure days to other Factor VIII products (adolescent/adult subjects) or 50 exposure days to other Factor VIII products (pediatric subjects). A previously untreated patient was defined as a subject with a diagnosis of severe hemophilia A (FVIII activity level < 1%) based on medical records or central laboratory results with no prior use of purified Factor VIII containing clotting products (5 previous exposure days to blood components are acceptable). Total exposure of PTPs and PUPs to ESPEROCT® was 80,425 exposure days corresponding to 889 patient years of treatment and 18,184 exposure days corresponding to 234 patient years of treatment, respectively.

During the clinical trials in PTPs, adverse reactions occurred at a rate of 0.10 events per patient year of exposure. The most frequently reported adverse reactions were rash (5.2%), injection site reaction (2.6%), redness (1.9%), and itching (pruritus) (1.5%).

During the clinical trial in PUPs, adverse reactions occurred at a rate of 0.25 events per patient year of exposure. The most frequently reported adverse reactions were Factor VIII inhibition (30%), injection site reaction (2.5%), drug hypersensitivity (2.5%), redness (1.2%), and rash (1.2%).

6.2 Immunogenicity

In clinical trials with PTPs and PUPs, subjects were monitored for neutralizing and non-neutralizing antibodies to Factor VIII (Factor VIII inhibitor), and binding antibodies to Factor VIII or ESPEROCT®, polyethylene glycol (PEG), and or Chinese hamster ovary (CHO) host cell protein. **Table 3** summarizes the number of subjects with anti-drug antibodies in PTPs and PUPs.

Previously treated patients (PTPs)

Of the 270 subjects in the PTP trials, 1 (0.4%) subject developed confirmed neutralizing antibodies to Factor VIII (13.5 Bethesda Units). In addition, 2 (0.7%) subjects had transient low titer FVIII antibody (<5 Bethesda Units) test results at a single occasion. Anti-PEG antibodies of no clinical consequence were detected in 43 (15.9%) PTPs, 32 (11.9%) of whom had pre-existing anti-PEG antibodies. Nine (3.3%) subjects developed anti-CHO host cell protein antibodies of no clinical consequence [*see Warnings and Precautions (5.2)*].

Previously untreated patients (PUPs)

In a clinical trial in PUPs < 6 years of age, of the 80 treated subjects (excluding 1 subject with pre-existing Factor VIII inhibitors), 21 (26.3%) subjects developed Factor VIII inhibitors (≥ 0.6 Bethesda Units). Of 70 subjects with at least 10 exposure days to ESPEROCT® or previously confirmed Factor VIII inhibitors, 21 (30%) subjects developed inhibitors, 11 (15.7%) of whom developed high titer inhibitors (≥ 5 Bethesda Units) and 10 (14.3%) of whom developed low titer inhibitors (< 5 Bethesda Units). Of total 21 subjects with inhibitors, two (2) subjects with high-titer FVIII inhibitor discontinued the trial. Six (6) of the remaining subjects (3 with high-titer and 3 with low-titer) were switched to immune tolerance induction therapy and completed the treatment. Two (2) subjects with high-titer inhibitor remained inhibitor positive until the end of the trial [*see Warning and Precaution (5.2)*].

Of the 80 treated subjects, binding antibodies to Factor VIII or ESPEROCT®, anti-PEG IgM, anti-PEG IgG, and anti-CHO host cell protein antibodies were developed in 42 (52.5%), 22 (27.5%), 50 (62.5%), and 7 (8.8%) subjects, respectively, except subjects who had pre-existing antibodies. Higher incidence of non-neutralizing antibodies binding to Factor VIII or ESPEROCT® was observed in subjects with FVIII inhibitors (20/21, 95.2%) compared to subjects without inhibitors (22/59, 37.3%) whereas the development of anti-PEG IgM and IgG antibodies was not significantly different between inhibitor and non-inhibitor subjects.

6.2 Immunogenicity (cont'd)

Table 3: Incidences of anti-drug antibodies in PTPs and PUPs

	PTP (all age) (N=270) n (%)	PUP (< 6 years of age) (N=80) n (%)
FVIII neutralizing antibodies		
Confirmed inhibitor (≥ 0.6 BU)	1 (0.4)	21 (26.3)
High titer inhibitor (≥ 5 BU)	1 (0.4)	11 (13.8)
Low titer inhibitor (< 5 BU)	0	10 (12.5)
Anti-ESPEROCT®/FVIII binding antibodies		
Conversion to positive antibodies	4 (1.5)	42 (52.5)
Pre-existing antibodies	2 (0.7)	1 (1.3)
Anti-PEG IgM antibodies		
Conversion to positive antibodies	11 (4.1)	22 (27.5)
Pre-existing antibodies	32 (11.9)	16 (20)
Anti-PEG IgG antibodies		
Conversion to positive antibodies	NA	50 (62.5)
Pre-existing antibodies	NA	14 (17.5)
Anti-CHO host cell protein antibodies		
Conversion to positive antibodies	9 (3.3)	7 (8.8)
Pre-existing antibodies	2 (0.7)	2 (2.5)

Note: "Conversion to positive antibodies" refers only to patients who were not detected with positive antibodies at baseline but developed antibodies post-baseline.
"Pre-existing antibodies" refers to patients who were detected with positive antibodies at baseline.
NA: Not analyzed.

6.2 Immunogenicity (cont'd)

In PUPs, high titers of anti-PEG IgG antibodies were associated with low Factor VIII incremental recovery (IR). In the PUP trial, a decreased Factor VIII IR, defined as at least 2 consecutive measurements of <0.6 (IU/dL)/(IU/kg) at 30 min post-dose, was identified after exposure to ESPEROCT® (5 EDs) in 17 out of 59 (28.8%) subjects without detectable Factor VIII inhibitors, which was observed with increased titers of anti-PEG IgG antibodies. As treatment of ESPEROCT® was continued, titers of anti-PEG IgG decreased and IR returned to ≥ 0.6 (IU/dL)/(IU/kg) between 15 to 70 EDs to ESPEROCT®. A post hoc subgroup analysis indicated that subjects with decreased IR may have an increased bleeding tendency during the decreased IR period [*see Warning and Precaution (5.3)*].

The detection of antibodies is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval of ESPEROCT®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Decreased Factor VIII activity: There have been reports of decreased Factor VIII activity in the absence of detectable Factor VIII inhibitors in previously treated patients (PTPs) upon switching to ESPEROCT® from other Factor VIII products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with ESPEROCT® use in pregnant women to determine whether there is a drug-associated risk. Animal reproduction studies have not been conducted with ESPEROCT®. It is unknown whether ESPEROCT® can cause fetal harm when administered to a pregnant woman or can affect fertility.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ESPEROCT® in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESPEROCT® and any potential adverse effects on the breastfed infant from ESPEROCT® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ESPEROCT® have been established for pediatric patients for the treatment and control of bleeding episodes, perioperative management, and routine prophylaxis use.

Safety and efficacy were evaluated in 93 PTPs <18 years of age, [*see Adverse Reactions (6) and Clinical Studies (14)*]. Of the PTPs, 34 (36.6%) were 1 to <6 years of age; 34 (36.6%) were 6 to <12 years of age; and 25 (27%) were 12 to <18 years of age. Pharmacokinetic parameters were evaluated for 27 PTPs who were treated with ESPEROCT® [*see Clinical Pharmacology (12.3)*].

No difference in the safety profile of ESPEROCT® was observed between previously treated pediatric subjects and adult subjects. Pharmacokinetic studies in children <12 years of age demonstrated higher clearance, a shorter half-life, and lower incremental recovery of Factor VIII compared to adults, but the pharmacokinetic parameters are comparable between young children (1–<6 years) and older children (6–<12 years). Because clearance (per kg body weight) is higher in children (<12 years), a higher dose and more frequent dosing may be needed in this population [*see Clinical Pharmacology (12.3)*].

Safety including immunogenicity was evaluated in 81 PUPs <6 years of age who received at least one dose of ESPEROCT® [*see Adverse Reactions (6.1, 6.2)*].

8.5 Geriatric Use

Clinical studies of ESPEROCT® did not include sufficient numbers of subjects age 65 years and over to determine whether or not they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and other drug therapy.

11 DESCRIPTION

ESPEROCT® is a sterile, preservative-free, non-pyrogenic lyophilized powder for intravenous injection after reconstitution with the provided saline diluent. The active ingredient in ESPEROCT® is a recombinant analogue of human coagulation Factor VIII (FVIII) conjugated with a 40-kDa polyethylene glycol (PEG) molecule. ESPEROCT® is formulated with the following excipients: sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, and calcium chloride.

FVIII activity in ESPEROCT® is determined using the chromogenic assay described in the European Pharmacopoeia. The activity assignment employs a FVIII reference material that is traceable to the current World Health Organization (WHO) international standard for FVIII concentrate, and evaluated by appropriate methodologies to ensure the accuracy of the results. ESPEROCT® is available in single-dose vials that contain nominally 500, 1000, 1500, 2000, or 3000 IU of FVIII. Each vial of ESPEROCT® is labeled with the actual FVIII activity. After reconstitution with the supplied diluent (0.9% saline), each mL of the solution contains approximately 125, 250, 375, 500, or 750 IU of FVIII, respectively.

The FVIII protein in ESPEROCT® is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology, and contains a truncated B domain, which is O-glycosylated. The polypeptide part of the molecule has a molecular mass of 166 kDa (calculated excluding post-translational modifications) and represents a heterodimer of a heavy chain and a light chain, which are held together by non-covalent interactions. The recombinant FVIII protein is purified using a series of chromatographic steps, one of which is affinity chromatography, with the use of a monoclonal antibody to selectively isolate the rFVIII from the cell culture medium. The 40-kDa PEG molecule is conjugated to the O-glycan moiety of the B domain using an enzymatic reaction to produce a glycopegylated FVIII (FVIII-PEG). The purification process includes two viral clearance steps, namely detergent (Triton X-100) treatment for inactivation of enveloped viruses, and 20-nm filtration for removal of enveloped and non-enveloped viruses. No additives of human or animal origin are used during the manufacturing process and formulation of ESPEROCT®.

In the blood circulation, when FVIII-PEG is activated by thrombin, the B-domain portion with the attached PEG moiety is cleaved off, and the resulting activated FVIII (FVIIIa) is similar in structure and function to native FVIIIa.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ESPEROCT®, a glycopegylated form of recombinant anti-hemophilic factor, temporarily replaces the missing coagulation Factor VIII needed for effective hemostasis in congenital hemophilia A patients. The Factor VIII in ESPEROCT® is conjugated to a 40-kDa polyethylene glycol molecule which increases the half-life and decreases the clearance compared to the non-pegylated molecule.

12.2 Pharmacodynamics

The administration of ESPEROCT® increases plasma levels of Factor VIII and can temporarily correct the coagulation defect in hemophilia A patients, as reflected by a decrease in activated partial thromboplastin time (aPTT).

12.3 Pharmacokinetics

All pharmacokinetic studies with ESPEROCT® were conducted in previously treated subjects with severe hemophilia A (Factor VIII<1%). In total, 129 single-dose pharmacokinetic profiles of ESPEROCT® were evaluated in 86 subjects (including 24 pediatric subjects, 1–<12 years).

12.3 Pharmacokinetics (cont'd)

Table 4 shows data for subjects who each received a single dose of 50 IU/kg. The plasma samples were analyzed using the one-stage clotting assay. There was a trend of increasing incremental recovery and AUC, and decreasing clearance, with age.

Table 4: Single-dose PK parameters of ESPEROCT® 50 IU/kg, by age, using one-stage clotting assay (geometric mean (CV%))

PK Parameter No. of subjects	1 to <6 years N=12	6 to <12 years N=10	12 to <18 years N=3	>18 years N=42
No. of profiles	12	10	5	78
IR (IU/dL) per (IU/kg)[a]	1.82 (32)	1.67 (22)	2.45 (16)	2.53 (24)
FVIII recovery (IU/dL)[a]	103.2 (27)	98.7 (18)	117.7 (14)	130.4 (26)
$t_{1/2}$ (hours)	14.7 (27)	13.8 (32)	17.4 (39)	21.7 (33)
AUC_{inf} (IU*hour/dL)	2305 (42)	2197 (38)	3063 (40)	4110 (38)
CL (mL/hour/kg)	2.4 (42)	2.7 (42)	1.6 (39)	1.2 (34)
Vss (mL/kg)	44.2 (25)	47.3 (28)	36.4 (12)	37.3 (26)
MRT (hours)	18.1 (27)	17.8 (35)	23.4 (43)	27.4 (28)[b]

PK parameters are presented in geometric mean.
Abbreviations: IR = Incremental recovery; $t_{1/2}$ = terminal half-life; AUC = area under the FVIII activity time profile; CL = clearance; Vss = volume of distribution at steady-state; MRT = mean residence time; CV% = coefficient of variation.
[a]IR and FVIII recovery were assessed 30 minutes post-dosing 50 IU/kg for patients ≥12 years and 60 minutes post-dosing 50 IU/kg (first sample) for children <12 years.
[b]Calculation based on 64 profiles.

12.3 Pharmacokinetics (cont'd)

In the single-dose PK assessment in adult subjects, whose body mass index (BMI) ranged from 17-35 kg/m^2, differences were noted for individuals who were overweight (BMI 25 – <30 kg/m^2) and obese (BMI 30 – <35 kg/m^2). Incremental recovery was increased by approximately 17% and 41%, AUC was increased by approximately 10% and 27%, and clearance was decreased by approximately 8% and 23% respectively, all in comparison to those subjects with BMI <25 kg/m^2. There is insufficient data to recommend specific dose adjustments for overweight and obese patients. The dose may be adjusted as necessary per prescriber's discretion.

Observed pre-dose (trough) and post-dose (peak) plasma Factor VIII activity levels at steady-state during prophylactic treatment with ESPEROCT® are presented in **Table 5** by dose regimen and age range.

Table 5: Steady-state trough and peak plasma FVIII activity by age and dose regimen, chromogenic assay (geometric mean [95% CI])

Dose Regimen	60 IU/kg twice weekly** (50–75 IU/kg)		50 IU/kg Q4D*		75 IU/kg Q7D*	
Age range No. patients	<6 years N=31	6–<12 years N=34	12–<18 years N=23	≥18 years N=143	12–<18 years N=6	≥18 years N=29
Trough, IU/dL	1.2 (0.8; 1.6)	2.0 (1.5; 2.7)	2.7 (1.8; 4.0)	3.0 (2.6; 3.5)	0.6 (0.2; 1.6)	1.3 (0.9; 2.0)
Peak, IU/dL	125.0 (118.7; 131.6)	143.3 (136.8; 150.2)	125.1 (116.0; 135.0)	137.9 (133.9; 142.2)	198.0 (166.8; 235.2)	197.9 (184.9; 212.7)

*Data included in analysis: adolescents/adults Main Phase until Visit 8 (end of the Main Phase) 50 IU/kg Q4D, and extension 1 for 75 IU/kg Q7D. Only measurements collected at steady-state for the given prophylaxis treatment are included in the analyses.
**Data included in analysis: pediatric Main Phase 60 IU/kg (50–75 IU/kg) twice weekly. Only measurements collected at steady-state for the given prophylaxis treatment are included in the analyses.

Time of Factor VIII Activity Above 5%

Steady-state Factor VIII activity profiles were estimated using a one-compartment model with first-order elimination with PK parameters of clearance (CL) and volume of distribution (**Table 6**). Pharmacokinetic predictions showed that in all age groups, patients dosed twice weekly (dosing interval alternating between 3 and 4 days) or Q4D will be above 5% Factor VIII activity (i.e., in the range of mild hemophilia) for the majority of time (72–95% of time). Patients dosed with 50 IU/kg every 4 days will be above 1% Factor VIII activity 100% of the dosing interval. Patients dosed with 75 IU/kg every 7 days are predicted to be above 5% for 57% of time and above 1% for 83% of time.

12.3 Pharmacokinetics (cont'd)

Table 6: Estimation of steady-state peak and trough FVIII activity and time to 5% FVIII activity for ESPEROCT®

Dose regimen Age range	60 IU/kg (50–75 IU/kg) twice weekly <12 years	50 IU/kg twice weekly ≥12 years	50 IU/kg Q4D ≥12 years	75 IU/kg Q4D ≥12 years
Peak FVIII activity (%)	110/112*	133/138*	132	194
Trough FVIII activity (%)	2.8/0.8*	8.6/3.6*	3.5	0.3
Time to 5% FVIII activity (days)	2.5/2.5*	3.6/3.6*	3.6	4.0
% of time in dosing interval above 5% FVIII activity	72	95	90	57

*Twice weekly values are shown as 3 day/4 day. Only 50 IU/kg data are used for the analysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and impairment of fertility studies in animals have not been performed.

13.2 Animal Toxicology and/or Pharmacology

No adverse effects were observed in immune-deficient rats intravenously injected with ESPEROCT® (50-1200 IU/kg/injection), once every 4th day for 52 weeks. No evidence of polyethylene glycol accumulation was detected by immunohistochemical staining of brain tissue, including the choroid plexus.

14 CLINICAL STUDIES

The safety and efficacy of ESPEROCT® have been evaluated in five multinational, open-label trials in male subjects with severe hemophilia A (<1% endogenous Factor VIII activity). One trial was subsequently partially randomized to evaluate two different prophylaxis regimens. All subjects were previously treated, which was defined as having received other Factor VIII products for ≥150 exposure days for adolescents and adults, and ≥50 exposure days for pediatric subjects. The key exclusion criteria across trials included known or suspected hypersensitivity to trial or related products and known history of Factor VIII inhibitors or current inhibitor ≥0.6 Bethesda units (BU).

14 CLINICAL STUDIES (cont'd)

The efficacy evaluation included 254 subjects, who received at least one dose of ESPEROCT®, in the following trials:

- Adolescent/adult trial: This trial included 186 subjects, 161 adults (18 to 65 years old) and 25 adolescents (12 to <18 years old); it consisted of a Main Phase and optional Extension Phase. During the Main Phase, 175 subjects received the prophylaxis regimen which consisted of 50 IU/kg every 4 days (Q4D), while 12 adults chose to be treated on-demand. (One subject changed from on-demand to prophylaxis and is counted in both groups.) Thirteen (7%) of 175 adults in the prophylaxis arm modified their dosing regimen to Q3-4D dosing for ease of use. All subjects received at least one dose of ESPEROCT® and are evaluable for safety and efficacy. A total of 165 subjects (91%) completed the Main Phase of this trial.
  - Extension: This extension compared two dose regimens: 75 IU/kg every 7 days (Q7D) and 50 IU/kg Q4D. The randomization was open to subjects who experienced 2 or fewer bleeds during the last 6 months in the Main Phase.
- Pediatric trial: This trial of PTPs included 68 subjects who were evenly divided with 34 in each age group, 0–<6 and 6–<12 years of age. All subjects received the same prophylaxis regimen of approximately 65 IU/kg (50–75 IU/kg) twice weekly. A total of 63 subjects (93%) completed the Main Phase.
- Surgery trial: In the surgery trial, 33 previously treated adolescents/adults underwent 45 major surgeries. The dose level of ESPEROCT® was chosen so that FVIII activity at least as recommended by World Federation of Hemophilia (WFH) guidelines was targeted. All subjects returned to the adolescent/adult trial after the surgery trial assessments were completed.

On-demand Treatment and Control of Bleeding Episodes

There were 1506 bleeds reported in 171 of 254 subjects across the completed clinical trials, and the most common bleed types were joint (65.2%), muscle (14.5%), and subcutaneous (8.9%). **Table 7** summarizes the efficacy in control of bleeding episodes by age.

Doses used for treatment of bleeding episodes depended on age, treatment regimen and the severity of the bleed.

Of the 1407 mild and moderate bleeding episodes in all subjects in the adolescent/adult study, the median dose used was 42 IU/kg. For subjects who were on the on-demand arm the median initial dose was 28 IU/kg and 88.4% of the bleeds were treated successfully with a single dose. In subjects receiving routine prophylaxis, the median initial dose was 52 IU/kg, and 76.4% of the bleeds were successfully treated with a single dose. Of the 15 severe bleeds, 12 (80%) required more than one dose with a total median dose of 111 IU/kg.

In the pediatric study, 70 mild/moderate bleeds in children <12 years old receiving routine prophylaxis were treated with a median initial dose of 64 IU/kg per injection, with 63% treated with a single injection. When needed, additional median doses of 62 IU/kg were used at approximately 24 hour intervals. The median total dose was 70 IU/kg per bleed.

14 CLINICAL STUDIES (cont'd)

Table 7: Summary of efficacy in control of bleeding episodes by age

Age range # of subjects		<6 years N=34	6 – <12 years N=34	12 – <18years N=25	≥18 years N=161	Total N= 254
# of bleeds		30	40	112	1324	1506
# of injections	**1–2**	76.7%	82.5%	88.4%	95.5%	94.3%
	>2	23.3%	17.5%	11.6%	4.5%	5.7%
Response to first treatment	**Excellent/ Good**	80.0%	77.5%	75.0%	88.7%	87.3%
	Moderate	13.3%	17.5%	17.9%	10.3%	11.1 %

Definition of Hemostatic Response:
Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection.
Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after one injection, but possibly requiring more than one injection for complete resolution.
Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection; usually requiring more than one injection.

Perioperative Management

The efficacy analysis of ESPEROCT® in perioperative management included 45 major surgical procedures performed in 33 adolescent and adult subjects. The procedures included 15 joint replacements, 9 arthroscopic orthopedic interventions, 17 other orthopedic interventions, and 4 non-orthopedic surgeries.

The clinical evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or none. The hemostatic effect of ESPEROCT® was rated as "excellent" or "good" in 43 of 45 surgeries (95.6%), while the effect was rated as "moderate" in 2 surgeries (4.4%). No surgery had an outcome rated as "none" or "missing."

The median pre-operative dose for adults and adolescents undergoing major surgeries was 52 IU/kg, and the median total dose was 702 IU/kg. During post-operative days 1-6, the median dose was 32 IU/kg at approximately 24 hour intervals. During post-operative days 7-14, the median dose was 36 IU/kg at approximately 28 hour intervals. The number of doses and duration of treatment varied by procedure.

Routine Prophylaxis in Adolescents/Adults

The efficacy of ESPEROCT® in routine prophylaxis with Q4D dosing was demonstrated for the adult/adolescent population (see **Table 8**). In the extension part of the study, treatment success of the Q7D arm was not established. During the Main Phase of the adolescent/adult trial, 186 subjects had a total of 159 exposure years. The median annualized bleeding rate (ABR) for treated bleeds in adults and adolescents treated every 4 days was 1.2 (IQR: 0.0:4.3), and mean ABR was 3.0 (SD: 4.7). When including all bleeds (treated and non-treated), the median ABR was 1.2 (IQR: 0.0; 4.7) and the mean ABR was 3.3 (SD: 4.9).

14 CLINICAL STUDIES (cont'd)

Table 8: Efficacy in adolescent/adult prophylaxis, median and mean ABRs by age, treatment regimen, and bleed type

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	25	150	175	12
Mean treatment duration (years)	0.85	0.81	0.82	1.33
Treated bleeds				
# of subjects with bleeds (%)	19 (76)	86 (57)	105 (60)	12 (100)
# of subjects without bleeds (%)	6 (24)	64 (43)	70 (40)	0
# of bleeds	67	369	436	532
Median ABR (IQR)	2.2 (0.9;4.7)	1.2 (0.0;3.7)	1.2 (0.0;4.3)	30.9 (18.6;38.5)
Mean ABR (SD)	3.5 (3.9)	2.9 (4.8)	3.0 (4.7)	31.9 (19.1)
All bleeds (treated and untreated)				
# of subjects with bleeds (%)	19 (76)	88 (59)	107 (61)	12 (100)
# of subjects without bleeds (%)	6 (24)	62 (41)	68 (39)	0
# of bleeds*	72	386	458	536
Median ABR (IQR)	2.2 (0.9;6.0)	1.2 (0.0;4.3)	1.2 (0.0;4.7)	31.3 (18.6;38.9)
Mean ABR (SD)	3.7 (4.1)	3.2 (5.1)	3.3 (4.9)	32.2 (19.1)
Treated spontaneous bleeds				
# of subjects with bleeds (%)	11 (44)	65 (43)	76 (43)	12 (100)
# of subjects without bleeds (%)	14 (56)	85 (57)	99 (57)	0
# of bleeds	30	221	251	415
Median AsBR (IQR)	0.0 (0.0;1.5)	0.0 (0.0;1.9)	0.0 (0.0;1.8)	19.4 (12.1;31.0)
Mean AsBR (SD)	1.4 (2.4)	1.8 (3.7)	1.7 (3.5)	24.5 (17.3)
Treated traumatic bleeds				
# of subjects with bleeds (%)	16 (64)	57 (38)	73 (42)	10 (83)
# of subjects without bleeds (%)	9 (36)	93 (62)	102 (58)	2 (17)
# of bleeds	37	146	183	110
Median AtBR (IQR)	1.3 (0.0;2.6)	0.0 (0.0;1.4)	0.0 (0.0;1.7)	4.3 (0.8;9.9)
Mean AtBR (SD)	2.1 (2.9)	1.1 (2.2)	1.2 (2.3)	6.1 (6.2)
Treated joint bleeds				
# of subjects with bleeds (%)	16 (64)	74 (49)	90 (51)	12 (100)
# of subjects without bleeds (%)	9 (36)	76 (51)	85 (49)	0
# of bleeds	37	288	325	309
Median AjBR (IQR)	1.2 (0.0;2.8)	0.0 (0.0;2.8)	0.9 (0.0;2.8)	19.4 (4.5;28.8)
Mean AjBR (SD)	1.8 (2.2)	2.3 (4.3)	2.2 (4.1)	19.7 (15.1)

ABR = annualized bleed rate; IQR = interquartile range, 25th percentile to 75th percentile; SD = standard deviation; AsBR = annualized spontaneous bleed rate; AtBR = annualized traumatic bleed rate; AjBR = annualized joint bleed rate.
*Reflects all bleeds reported by patients including those where no ESPEROCT® was administered.

14 CLINICAL STUDIES (cont'd)

Routine Prophylaxis in Children <12 Years of Age

Overall, 68 children below 12 years received prophylactic treatment with ESPEROCT® at an average dose of approximately 65 IU/kg twice weekly. The prophylactic effect of ESPEROCT® was demonstrated with a median ABR rate of 2.0 (IQR: 0.0; 2.8) and 2.0 (IQR: 0.0; 4.2) for treated bleeds and all bleeds respectively (see **Table 9**). The mean ABR (SD) for treated bleeds and all bleeds were 3.1 (7.1) and 4.4 (8.7), respectively. Of the 68 children, 22 (32%) did not experience any bleeding episodes and 29 (43%) did not experience any bleeding episodes that required treatment during the Main Phase of the trial. Of the 13 subjects with 17 documented target joints at baseline, 10 subjects (77%) and 14 target joints (82%) did not have any bleeds during the Main Phase of the trial.

14 CLINICAL STUDIES (cont'd)

Table 9: Efficacy in pediatric prophylaxis, median and mean ABR by age and bleed type

	Prophylaxis Regimen		
Age range	**<6 years****	**6 to <12 years**	**0 to <12 years**
# of subjects	N=34	N=34	N=68
Mean treatment duration (years)	0.46	0.51	0.48
Treated bleeds			
# of subjects with bleeds (%)	19 (56)	20 (59)	39 (57)
# of subjects without bleeds (%)	15 (44)	14 (41)	29 (43)
# of bleeds	30	40	70
Median ABR (IQR)	1.9 (0.0;2.1)	2.0 (0.0;3.9)	2.0 (0.0;2.8)
Mean ABR (SD)	3.9 (9.7)	2.3 (2.9)	3.1 (7.1)
All Bleeds (treated and untreated)			
# of subjects with bleeds (%)	20 (59)	26 (77)	46 (68)
# of subjects without bleeds (%)	14 (41)	8 (24)	22 (32)
# of bleeds*	41	65	106
Median ABR (IQR)	2.0 (0.0;4.0)	2.0 (1.9;6.0)	2.0 (0.0;4.2)
Mean ABR (SD)	5.0 (11.9)	3.8 (3.6)	4.4 (8.7)
Treated spontaneous bleeds			
# of subjects with bleeds (%)	6 (18)	7 (21)	13 (19)
# of subjects without bleeds (%)	28 (82)	27 (79)	55 (81)
# of bleeds	9	10	19
Median AsBR (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Mean AsBR (SD)	2.1 (7.3)	0.6 (1.5)	1.3 (5.3)
Treated traumatic bleeds			
# of subjects with bleeds (%)	15 (44)	17 (50)	32 (47)
# of subjects without bleeds (%)	19 (56)	17 (50)	36 (53)
# of bleeds	20	30	50
Median AtBR (IQR)	0.0 (0.0;2.0)	0.9 (0.0;2.0)	0.0 (0.0;2.0)
Mean AtBR (SD)	1.7 (4.0)	1.7 (2.5)	1.7 (3.3)
Treated joint bleeds			
# of subjects with bleeds (%)	7 (21)	12 (35)	19 (28)
# of subjects without bleeds (%)	27 (79)	22 (65)	49 (72)
# of bleeds	10	24	34
Median AjBR (IQR)	0.0 (0.0;0.0)	0.0 (0.0;2.0)	0.0 (0.0;2.0)
Mean AjBR (SD)	1.5 (6.3)	1.4 (2.4)	1.5 (4.7)

ABR = annualized bleed rate; IQR = interquartile range, 25th percentile to 75th percentile; SD = standard deviation; AsBR = annualized spontaneous bleed rate; AtBR = annualized traumatic bleed rate; AjBR = annualized joint bleed rate.
*Reflects all bleeds reported by patients including those where no ESPEROCT® was administered.
**Elevated mean ABRs are due to subjects who withdrew from the study, whose bleeding rates were extrapolated to one year.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- ESPEROCT® is supplied in packages comprised of a single-dose vial containing nominally 500, 1000, 1500, 2000 or 3000 IU of Factor VIII activity; a MixPro® pre-filled diluent syringe containing 0.9% saline solution; and a sterile vial adapter with a 25-micrometer filter, which serves as a needleless reconstitution device.
- The actual Factor VIII activity in IU is stated on each ESPEROCT® carton and vial label.

16 HOW SUPPLIED/STORAGE AND HANDLING (cont'd)

Table 10: ESPEROCT® Presentations

Nominal Dosage Strength	Cap Color Indicator	Carton NDC Number	Components
500 IU	Red	NDC 0169 8500 01	• ESPEROCT® in single-dose vial [NDC 0169 8501 11] • Pre-filled syringe with 4 mL sterile saline diluent [NDC 0169 8008 98] • Vial adapter
1000 IU	Green	NDC 0169 8100 01	• ESPEROCT® in single-dose vial [NDC 0169 8101 11] • Pre-filled syringe with 4 mL sterile saline diluent [NDC 0169 8008 98] • Vial adapter
1500 IU	Gray	NDC 0169 8150 01	• ESPEROCT® in single-dose vial [NDC 0169 8151 11] • Pre-filled syringe with 4 mL sterile saline diluent [NDC 0169 8008 98] • Vial adapter
2000 IU	Yellow	NDC 0169 8200 01	• ESPEROCT® in single-dose vial [NDC 0169 8201 11] • Pre-filled syringe with 4 mL sterile saline diluent [NDC 0169 8008 98] • Vial adapter
3000 IU	Black	NDC 0169 8300 01	• ESPEROCT® in single-dose vial [NDC 0169 8301 11] • Pre-filled syringe with 4 mL sterile saline diluent [NDC 0169 8008 98] • Vial adapter

IU = International Units.

novo nordisk®

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Please click here for Prescribing Information.

esperoct®
antihemophilic factor (recombinant), glycopegylated-exei

16 HOW SUPPLIED/STORAGE AND HANDLING (cont'd)

- The ESPEROCT® vials are made of glass, closed with a chlorobutyl rubber stopper (not made with natural rubber latex), and sealed with an aluminum cap.
- The pre-filled diluent syringes are made of glass with a siliconized bromobutyl rubber plunger (not made with rubber latex).
- The closed vials and pre-filled diluent syringes are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Storage and Handling

- Store ESPEROCT® in the original package to protect the ESPEROCT® vial from light.
- Store ESPEROCT® in a powder form under refrigeration at 36°F to 46°F (2°C to 8°C) for up to 30 months from the date of manufacture until the expiration date stated on the label. During the 30-month shelf life, ESPEROCT® may be kept at room temperature:
  - up to 86°F (30°C) for no longer than 12 months,

    or
  - up to 104°F (40°C) for no longer than 3 months
- Record the date on the carton when the product was removed from the refrigerator. Do not return the product to the refrigerator.
- Do not freeze ESPEROCT®.
- Use ESPEROCT® within 4 hours after reconstitution when stored at ≤86°F (30°C) or within 24 hours when stored in the refrigerator. Store the reconstituted product in the vial.
- Discard any unused reconstituted product.

Please see Important Safety Information on page 34.
Please click here for Prescribing Information.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- That allergic-type hypersensitivity reactions or anaphylaxis are possible with use of ESPEROCT®. Inform patients of the early signs of hypersensitivity reactions including rash, hives, itching, facial swelling, tightness of the chest, and wheezing. Advise patients to discontinue use of ESPEROCT® immediately and contact their healthcare provider and/or seek emergency care promptly if these symptoms occur.
- To contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII replacement therapy, as this may be a manifestation of an inhibitor.

Version: 4
License Number: 1261

For information contact:
Novo Nordisk Inc.
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Plainsboro, NJ 08536, USA
1-800-727-6500

Manufactured by:
Novo Nordisk A/S
Novo Allé, DK-2880 Bagsvaerd

Please see Important Safety Information on page 34.
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esperoct®
antihemophilic factor (recombinant), glycopegylated-exei

SECTION III: Distribution and Administration

Distribution of ESPEROCT®

ESPEROCT® is a specialty pharmaceutical product. ESPEROCT® can be accessed and distributed through specialty pharmacy distributors and hemophilia home care agencies.

Administration of ESPEROCT®

ESPEROCT® is self-administered by intravenous injection. Patients may infuse ESPEROCT® at a hemophilia treatment center, at a health care provider's office, or at home. Patients should not attempt to do self-infusion unless they are taught by their health care provider or hemophilia center.

Indications and Usage

ESPEROCT® [antihemophilic factor (recombinant), glycopegylated-exei] is indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes

- ESPEROCT® is not indicated for the treatment of von Willebrand disease

Important Safety Information

Contraindications

- Do not use in patients who have known hypersensitivity to ESPEROCT® or its components, including hamster proteins

Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis, may occur. Should hypersensitivity reactions occur, discontinue ESPEROCT® and administer appropriate treatment
- Development of neutralizing antibodies (inhibitors) has occurred. Perform an assay that measures Factor VIII inhibitor concentration if bleeding is not controlled with the recommended dose of ESPEROCT® or if the expected plasma Factor VIII activity levels are not attained
- Temporary decrease in Factor VIII incremental recovery (IR) has been observed after ESPEROCT® infusion, within the first 5 exposure days, in previously untreated patients (PUPs) <6 years of age. During the decreased IR period, these subjects may have an increased bleeding tendency. If bleeding is not controlled with the recommended dose of ESPEROCT® and/or the expected Factor VIII activity levels are not attained and Factor VIII inhibitors are not detected, consider adjusting the dose, dosing frequency, or discontinuing ESPEROCT®

Adverse Reactions

- The most frequently reported adverse reactions in clinical trials (≥1%) were rash, redness, itching (pruritus), and injection site reactions. Additional frequently reported adverse reactions (≥1%) in PUPs included Factor VIII inhibition and hypersensitivity

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esperoct®
antihemophilic factor (recombinant), glycopegylated-exei

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