Product Information Form for Hospitals

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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esperoct®
antihemophilic factor (recombinant), glycopegylated-exei

Product Information Form for Hospitals

1 AHFS CLASSIFICATION NUMBER

20:28.16

2 GENERIC NAME

Antihemophilic Factor (Recombinant), glycopegylated-exei

3 SOURCE OF SUPPLY

ESPEROCT® is manufactured by Novo Nordisk A/S.

4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

BL 125671/0, February 19, 2019

5 PHYSICAL PROPERTIES

a. Macroscopic appearance

ESPEROCT® is supplied as white to off-white lyophilized powder in single-dose vials, one vial per carton. The diluent for reconstitution of ESPEROCT® is 0.9% saline solution and is supplied in a pre-filled diluent syringe. ESPEROCT® is available in single-dose vials that contain nominally 500, 1000, 1500, 2000 or 3000 IU per vial.

b. Solubility

ESPEROCT® is formulated as a sterile, preservative-free, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% saline).

6 CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

The active ingredient in ESPEROCT® is a recombinant (r) analogue of human coagulation factor VIII (FVIII) conjugated with a 40-kDa polyethylene glycol (PEG) molecule. 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 40-kDa PEG molecule is conjugated to the O-glycan moiety of the FVIII B domain to produce a glycopegylated FVIII. Once activated, the B-domain portion with the attached PEG moiety is cleaved off, and the resulting rFVIIIa has a comparable structure to endogenous FVIIIa.

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6 CHEMICAL PROPERTIES (cont'd)

b. Recommended storage conditions for ESPEROCT®

Store ESPEROCT® in the original package in order to protect from light.

Store ESPEROCT® in a powder form under refrigeration at a temperature of 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.

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.

c. Excipients contained in the commercially available product

ESPEROCT® is formulated with the following excipients: sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, and calcium chloride.

The product contains no preservative.

7 PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

ESPEROCT® is a hemostatic agent.

b. Mechanism of action

ESPEROCT® temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

c. Pharmacokinetic data

All pharmacokinetic studies with ESPEROCT® were conducted in previously treated patients 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).

The table below 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.

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

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)
$t_{½}$ (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]

[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.

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.

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 the following table by dose regimen and age range.

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

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. of 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.

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 (see Table below). 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.

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

Dose regimen	60 IU/kg (50–75 IU/kg) twice weekly	50 IU/kg twice weekly	50 IU/kg Q4D	75 IU/kg Q7D
Age range	<12 years	≥12 years	≥12 years	≥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 days/4 days. Only 50 IU/kg data are used for the analysis.

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8 DOSAGE RANGE

a. Dosage range and route of administration

ESPEROCT® is for intravenous injection after reconstitution only.

- 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.

On-demand treatment and control of bleeding episodes

A guide for dosing ESPEROCT® for on-demand treatment and control of bleeding episodes is provided in the following table.

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, intraabdominal or intrathoracic bleeding, fractures	50	65	Additional dose(s) may be administered approximately every 24 hours

8 DOSAGE RANGE (cont'd)

Perioperative management

The dose level and dosing intervals for surgery depend on the procedure and local practice. A guide for dosing ESPEROCT® during surgery (perioperative management) is provided in the following table.

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®.

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8 DOSAGE RANGE (cont'd)

b. Use in specific populations

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.

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.

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. 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®.

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.

Safety including immunogenicity was evaluated in 81 PUPs <6 years of age who received at least one dose of ESPEROCT®.

8 DOSAGE RANGE (cont'd)

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.

9 SAFETY

a. Adverse reactions, toxicities, and special precautions

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%).

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%).

9 SAFETY (cont'd)

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%).

Immunogenicity

In clinical trials with PTPs and PUPs, subjects were monitored for neutralizing antibodies to Factor VIII (Factor VIII inhibitor), and binding antibodies to Factor VIII or ESPEROCT®, polyethylene glycol (PEG), 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.

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.

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.

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9 SAFETY (cont'd)

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

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.

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9 SAFETY (cont'd)

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.

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.

b. Contraindications, Warnings and Precautions

Contraindications

ESPEROCT® is contraindicated in patients who have known hypersensitivity to ESPEROCT® or its components (including hamster proteins).

Warnings and precautions

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. 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.

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).

9 SAFETY (cont'd)

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.

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.

Monitoring laboratory tests

If monitoring of Factor VIII is performed, use a chromogenic or one-stage clotting assay appropriate for use with ESPEROCT®.

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.

c. List potential drug-drug interactions if deemed clinically significant

N/A

10 COMPARISONS

N/A

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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