

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

KOVALTRY®

Antihemophilic Factor (Recombinant)

Supplied with Vial Adapter

IV Injection 250, 500, 1000, 2000, 3000 IU/vial

Coagulation Factor FVIII

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Date of Initial Approval:
Jan 27, 2016

Date of Revision:
Mar 7, 2023

Submission Control Number: 263027

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RECENT MAJOR LABEL CHANGES

1. INDICATIONS, 1.1. Pediatrics	01/2022
7. WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics	01/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics.....	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	4
4 DOSAGE AND ADMINISTRATION	4
4.1 Dosing Considerations	4
4.2 Recommended Dose and Dosage Adjustment	5
4.3 Reconstitution.....	6
4.4 Administration	9
4.5 Missed Dose	9
5 OVERDOSAGE	9
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	9
7 WARNINGS AND PRECAUTIONS	10
7.1 Special Populations	11
7.1.1 Pregnant Women.....	11
7.1.2 Breast-feeding.....	11
7.1.3 Pediatrics.....	11
7.1.4 Geriatrics.....	11
8 ADVERSE REACTIONS	12
8.1 Adverse Reaction Overview	12
8.2 Clinical Trial Adverse Reactions	12
9 DRUG INTERACTIONS	14
9.4 Drug-Drug Interactions	14
9.5 Drug-Food Interactions.....	14
9.6 Drug-Herb Interactions	14

9.7 Drug-Laboratory Test Interactions.....	14
10 CLINICAL PHARMACOLOGY	14
10.1 Mechanism of Action	14
10.2 Pharmacodynamics.....	14
10.3 Pharmacokinetics.....	14
11 STORAGE, STABILITY AND DISPOSAL.....	18
12 SPECIAL HANDLING INSTRUCTIONS.....	18
PART II: SCIENTIFIC INFORMATION	19
13 PHARMACEUTICAL INFORMATION.....	19
14 CLINICAL TRIALS.....	20
14.1 Trial Design and Study Demographics	20
14.2 Study Results.....	22
15 MICROBIOLOGY.....	26
16 NON-CLINICAL TOXICOLOGY.....	26
PATIENT MEDICATION INFORMATION.....	29

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KOVALTRY (Antihemophilic Factor [Recombinant]) is indicated for use in adults and children with hemophilia A for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of episodic bleeding
- Peri-operative management (surgical prophylaxis)

KOVALTRY does not contain von Willebrand factor and is not indicated for the treatment of von Willebrand disease.

1.1 Pediatrics

Pediatrics (< 12 years of age): KOVALTRY is appropriate for use in pediatric patients. One safety and efficacy study has been performed in 51 previously treated patients (PTPs) aged from 1 to 12 years old and 43 previously untreated patients/minimally treated patients (PUPs/MTPs) <6 years of age. (see [4 DOSAGE AND ADMINISTRATION](#))

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies with KOVALTRY did not include patients aged 65 and over to be able to determine whether they respond differently from younger adults. As with any patient receiving rFVIII, dose selection for an elderly patient should be individualized.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#) section.
- Known hypersensitivity to mouse or hamster protein.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A (see [7 WARNINGS AND PRECAUTIONS](#)).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Each vial of KOVALTRY (Antihemophilic Factor [Recombinant]) has the rFVIII potency in international units based on the chromogenic assay methodology stated on the label. The reconstituted product must be administered intravenously. The product must be administered within 3 hours after reconstitution. It is recommended to use the administration set provided to minimize losses of product due to adsorption and volume retention. KOVALTRY should not be mixed with other medicinal products.

4.2 Recommended Dose and Dosage Adjustment

The dosages described below are presented as general guidance. The recommended dosing for KOVALTRY is based on the clinical trials (see [14 CLINICAL TRIALS](#)). The dosage of KOVALTRY required for hemostasis must be individualized according to the needs of the patient, the bleeding type, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors and the FVIII level desired. The course of therapy can be followed with FVIII level assays (see [4.2 Recommended Dose and Dosage Adjustment](#), Routine Prophylaxis).

The clinical effect of KOVALTRY is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more KOVALTRY than would be calculated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected FVIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory test. When an inhibitor is present, the dosage requirement for KOVALTRY is extremely variable and the dosage can be determined only by the clinical response.

Calculation of Dosage

On-demand treatment:

The in vivo percent increase in FVIII level can be estimated by multiplying the dose of rFVIII per kilogram of body weight (IU/kg) by 2%. This method of calculation is based on clinical findings by Abildgaard et al. and is illustrated in the following examples.

Equation 1 – Calculation of KOVALTRY Dosage (Expected % FVIII Increase)

$$\text{Expected \% FVIII increase} = \frac{(\# \text{ units administered}) \times 2\%/\text{IU/kg}}{\text{body weight (kg)}}$$

$$\text{Example for a 70 kg adult: } \frac{1400 \text{ IU} \times 2\%/\text{IU/kg}}{70 \text{ kg}} = 40\%$$

Equation 2 – Calculation of KOVALTRY Dosage (Dosage Required)

$$\text{Dosage required (IU)} = \frac{(\text{body weight (kg)}) \times (\text{desired \% FVIII increase})}{2\%/\text{IU/kg}}$$

$$\text{Example for a 15 kg child: } \frac{15 \text{ kg} \times 100\%}{2\%/\text{IU/kg}} = 750 \text{ IU required}$$

The usual single dose is 10-30 IU/kg body weight. Higher dosages are recommended for life threatening or major hemorrhages. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the general guidelines in [Table 1](#).

Table 1 - Guidance for control and prevention of bleeding episodes for children and adults

Hemorrhagic Event/Type of Surgery	FVIII Level Required (IU/dL)	Frequency of Doses (Hours)/Duration of Therapy (Days)
Minor Hemorrhage (Early hemarthrosis, minor muscle, oral bleeds)	20-40%	Repeat every 12 to 24 hours. At least 1 day, until bleeding episode is resolved or hemostasis is achieved
Moderate to Major Hemorrhage (More extensive hemarthrosis, muscle bleeding, or hematoma)	30-60%	Repeat infusion every 12-24 hours 3 to 4 days or more until bleeding episodes are resolved.
Life-Threatening Hemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved
Minor Surgery (including tooth extraction)	30-60	Every 24 hours, at least 1 day, until hemostasis is achieved
Major Surgery	80-100 (pre- and post-operative)	Repeat dose every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain FVIII activity of 30-60% (IU/dL).

Pharmacokinetic data in pediatric patients (<12 years of age) are available in 15 PTPs. (see 10.3 Pharmacokinetics) This information should be taken into account when dosing or following FVIII levels in such a population.

Routine Prophylaxis

Adults and Adolescents (>12 years of age): The recommended dose for routine prophylaxis is 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week.

Children ≤ 12 years old: The recommended dose for routine prophylaxis is 20 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements.

Immune Tolerance

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

4.3 Reconstitution

Parenteral Products:

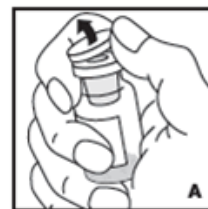
KOVALTRY powder should only be reconstituted with the supplied diluent (2.5 or 5.0 mL Sterile Water for Injection) using the prefilled syringe. Reconstitution should be performed in accordance with good practices rules, particularly with attention to asepsis.

If any component of the package is opened or damaged, do not use this component. The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Vial Adapter.

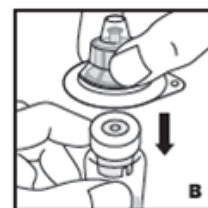
When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOVALTRY. KOVALTRY can be administered through an administration set without a filter since filtering is achieved through reconstitution with the Vial Adapter.

Always work on a clean surface and wash your hands before performing the following procedures:

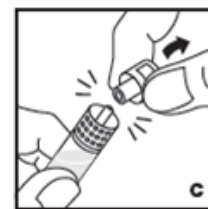
1. Warm both unopened vial and syringe in your hands to a comfortable temperature (do not exceed 37°C).
2. Remove protective cap from the vial (A). Aseptically cleanse the rubber stopper with alcohol, being careful not to handle the rubber stopper.



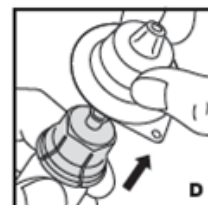
3. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.



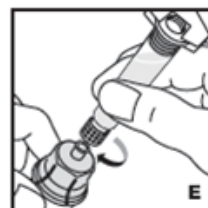
4. Holding the syringe by the barrel, snap the syringe cap off the tip (C). **Do not touch the syringe tip with your hand or any surface.** Set the syringe aside for further use.



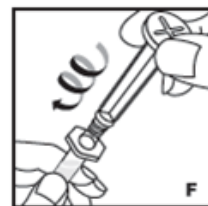
5. Now remove and discard the adapter plastic housing (D).



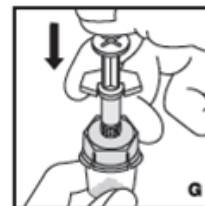
6. Attach the prefilled syringe to the vial adapter thread by turning clockwise (E).



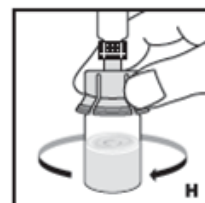
7. Remove the clear plastic plunger rod from the carton. Grasp the plunger rod by the top plate. **Avoid touching the sides and threads of the plunger rod.** Attach the plunger rod by turning it clockwise into the threaded rubber stopper of the prefilled syringe (F).



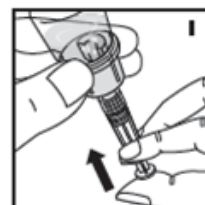
8. Inject the diluent **slowly** by pushing down on the plunger rod (G).



9. Swirl vial gently until all powder on all sides of the vial is dissolved (H). **Do not shake vial.** Be sure that all powder is completely dissolved. **Do not use if solution contains visible particles or is cloudy.**

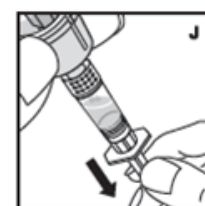


10. Push down on the plunger to push all air back into the vial. Then while holding the plunger down, turn the vial with syringe upside-down (invert) so the vial is now above the syringe (I).

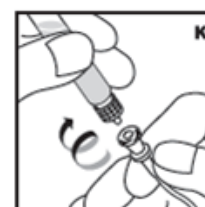


11. Withdraw all the solution into the syringe by pulling the plunger rod back slowly and smoothly (J). Tilt the vial to the side and back to make sure all the solution has been drawn toward the large opening in the rubber stopper and into the syringe.

Remove as much air as possible before removing the syringe from the vial by slowly and carefully pushing the air back into the vial.



12. Detach the syringe with plunger rod from the vial adapter by turning counter-clockwise. Attach the syringe to the administration set provided and inject intravenously (K). NOTE: follow instructions for infusion set provided.



If the dose requires more than one vial, reconstitute each vial as described above with the diluent syringe provided. Use a larger plastic syringe (not provided) to combine the content of the vials into the syringe.

Table 2 - Reconstitution of Parenteral Products

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
250 IU	2.5 mL	2.5 mL	100 IU/mL
500 IU	2.5 mL	2.5 mL	200 IU/mL
1000 IU	2.5 mL	2.5 mL	400 IU/mL
2000 IU	5.0 mL	5.0 mL	400 IU/mL
3000 IU	5.0 mL	5.0 mL	600 IU/mL

4.4 Administration

KOVALTRY (Antihemophilic Factor [Recombinant]) supplied with Vial Adapter is a needle-less system that prevents needlestick injuries during reconstitution (see [7 WARNINGS AND PRECAUTIONS](#)).

Administer KOVALTRY over several minutes. Adapt the rate of administration to the response of each individual patient. Similar to other rFVIII products, determine the pulse rate before and during administration of KOVALTRY. If there is a significant increase in pulse rate, reduce the rate of administration or temporarily halt the infusion allowing the symptoms to disappear promptly.

4.5 Missed Dose

Double doses are generally not required to compensate for forgotten individual doses.

Patients should be advised to proceed immediately with a regular administration of KOVALTRY and to continue treatment at regular intervals as required.

5 OVERDOSAGE

No symptoms of overdose have been reported.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous	Lyophilized powder for injection 250, 500, 1000, 2000, 3000 IU/vial	Calcium chloride Glycine Histidine Polysorbate 80 Sodium chloride Sucrose

KOVALTRY (Antihemophilic Factor [Recombinant]) is supplied in the following single use vials (see [Table 4](#)) and with a Vial Adapter. A prefilled diluent syringe containing Sterile Water for Injection, EP, USP for reconstitution, and a sterile administration set, are also provided.

Table 4 – KOVALTRY Vial Sizes

Approximate Factor VIII Activity	Diluent
250 IU	2.5 mL
500 IU	2.5 mL
1000 IU	2.5 mL
2000 IU	5.0 mL
3000 IU	5.0 mL

Each vial of KOVALTRY is labeled with actual recombinant Factor VIII activity expressed in IU determined using the chromogenic assay. This potency assignment employs a Factor VIII concentrate standard that is referenced to a WHO International Standard for Factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

KOVALTRY is a lyophilized powder and formulated with the following inactive ingredients /excipients for the final container: 2.2% glycine, 1% sucrose, 30 mM sodium chloride, 2.5 mM calcium chloride, 20 mM histidine and 80 ppm polysorbate 80. The pH of the reconstituted product is 6.6 to 7.0. KOVALTRY is available in 2.5 mL nominal fill volumes (for 250 IU, 500 IU, and 1000 IU nominal dosage strengths) and 5.0 mL nominal fill volumes (for 2000 IU, and 3000 IU nominal dosage strengths). The final product is a sterile, nonpyrogenic, preservative-free, powder preparation for intravenous (IV) injection.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

General

KOVALTRY (Antihemophilic Factor [Recombinant]) is intended for the treatment of bleeding disorders as a consequence of a deficiency in coagulation Factor VIII (FVIII). This deficiency should be confirmed prior to administering KOVALTRY.

Reconstitution, product administration, and handling of the administration set must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted KOVALTRY product in an appropriate container.

Catheter-related complications, such as local infections, bacteremia and catheter site thrombosis complications may be observed when KOVALTRY is administered via central venous access devices (CVADs). These complications have not been associated with the product itself.

Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY](#) for details.

Cardiovascular

Persons with hemophilia who have cardiovascular risk factors or diseases may be at the same risk of developing cardiovascular events as non hemophilic patients when clotting has been normalized by treatment with FVIII.

Immune

The formation of neutralizing antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with hemophilia A (see [Immunogenicity](#)). 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 Nijmegen-modified Bethesda assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to other genetic and environmental factors. The risk is highest in the first 20 exposure days. Rarely, inhibitors can develop after the first 100 exposure days.

In general, all patients treated with recombinant Factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Monitoring and Laboratory Tests

The clinical effect of KOVALTRY is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more rFVIII than was estimated in order to attain satisfactory clinical results (see [4 DOSAGE AND ADMINISTRATION](#)). If the calculated dose fails to attain the expected FVIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory tests. When an inhibitor is present, the dosage requirement for rFVIII is extremely variable and the dosage can be determined only by the clinical response.

Sensitivity/Resistance

Hypersensitivity reactions, including anaphylaxis are possible with KOVALTRY. The product may contain traces of hamster or mouse proteins which in some patients may cause allergic reactions.

Patients should be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension and nausea during infusion could constitute an early warning for hypersensitivity and anaphylactic reactions. Symptomatic treatment and therapy for hypersensitivity should be instituted as appropriate. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. In case of anaphylaxis, the current medical standards for treatment should be observed. Serious anaphylactic reactions require immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with KOVALTRY, as the patient population is almost exclusively male. Based on the very rare occurrence of hemophilia A in women, experience regarding the use of Factor VIII during pregnancy is not available. Therefore, Factor VIII should be used during pregnancy and lactation only if clearly indicated.

7.1.2 Breast-feeding

Based on the very rare occurrence of hemophilia A in women, experience regarding the use of Factor VIII during breast-feeding is not available. Therefore, Factor VIII should be used during pregnancy and lactation only if clearly indicated.

7.1.3 Pediatrics

Pediatric Use (< 12 years of age): KOVALTRY is appropriate for use in pediatric patients. One safety and efficacy study has been performed in 51 previously treated patients (PTPs) aged from 1 to 12 years old and 43 previously untreated patients/minimally treated patients (PUPs/MTPs) <6 years of age. In the clinical study of 43 PUPs/MTPs, the most frequently reported adverse reaction was Factor VIII inhibitor. (see [4 DOSAGE AND ADMINISTRATION](#), [14 CLINICAL TRIALS](#))

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Clinical studies with KOVALTRY did not include patients aged 65 and over to be able to determine whether they respond differently from younger adults. As with any patient receiving rFVIII, dose selection for an elderly patient should be individualized.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 236 (193 PTPs, 43 PUPs/MTPs) patients constituted the pooled safety population in the three phase III studies in previously treated patients (PTPs), previously untreated patients (PUPs) and minimal treated patients (MTPs); LEOPOLD I, LEOPOLD II, LEOPOLD Kids studies. The median time on clinical trial for the pooled safety population was 558 days (range 14 to 2436 days) with a median of 183 exposure days (EDs) (range 1 to 1230 EDs). A majority of patients (n= 201 of 236; 85.2%) accumulated \geq 100 EDs.

The total number of exposure days for all treatments (prophylaxis, on-demand, perioperative management, pharmacokinetic (PK) studies and immune tolerance induction was 65029 EDs, of which 59585 EDs were for prophylaxis treatment.

Subjects who received KOVALTRY for perioperative management with treatment period of 2 to 3 weeks (n=5) and those who received single doses of KOVALTRY for PK studies (n=6) were excluded from the pooled safety analysis (see [14 CLINICAL TRIALS](#)).

The most frequently reported adverse reactions in the pooled population were pyrexia (9.3%), headache (8.5%) and rash (5.5%). The most frequently reported adverse reaction in PUPs/MTPs was FVIII inhibitor (54.8%, 23/42) (see [Immunogenicity](#)).

8.2 Clinical Trial Adverse Reactions

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

The 236 patients (193 PTPs; 43 PUPs/MTPs, including 94 pediatric patients) were included to assess the frequency of adverse reactions in the three phase III studies LEOPOLD I, LEOPOLD II, and LEOPOLD Kids (see [Table 5](#)).

Table 5 – Adverse Drug Reactions from pooled clinical studies from all age groups (LEOPOLD I, LEOPOLD II, LEOPOLD Kids, N=236)

	KOVALTRY N (%)
Blood and Lymphatic System Disorders	
Lymphadenopathy	2 (0.8%)
Cardiac Disorders	
Palpitation	2 (0.8%)
Sinus tachycardia	2 (0.8%)
Gastrointestinal Disorders	
Abdominal pain	9 (3.8%)
Abdominal discomfort	3 (1.3%)
Dyspepsia	4 (1.7%)
General Disorders and Administration Site Conditions	
Chest discomfort	2 (0.8%)
Injection site reactions ^a	6 (2.5%)
Pyrexia	22 (9.3%)
Immune System Disorders^b	
Hypersensitivity	1 (0.4%)
Nervous System Disorders	
Dizziness	3 (1.3%)
Dysgeusia	1 (0.4%)
Headache	20 (8.5%)
Psychiatric Disorders	
Insomnia	5 (2.1%)
Skin and subcutaneous tissue disorders	
Dermatitis allergic	2 (0.8%)
Pruritus	6 (2.5%)
Rash ^c	13 (5.5%)
Urticaria	3 (1.3%)
Vascular disorders	
Flushing	1 (0.4%)

a includes injection site extravasation and hematoma, infusion site pain, pruritus, and swelling

b see [Immunogenicity](#) for Factor VIII inhibitors

c includes rash, rash erythematous, and rash pruritic, rash vesicular

In the LEOPOLD Kids Part B study in PUPs/MTPs (N=43) and extension (N=36), a different frequency than observed in LEOPOLD I, II, and Kids Part A in PTPs was detected for pyrexia (Kids Part B: 30.2%, n=13/43; extension: 30.6%, n=11/36) and Factor VIII inhibitors (Kids Part B: 54.8%, n=23/42; inhibitor analysis based on 42 out of 43 PUPs/MTPs, as one patient was unevaluable for inhibitor analysis and thus excluded). During the LEOPOLD Kids extension study, no patients developed a new Factor VIII inhibitor.

Immunogenicity

The immunogenicity of KOVALTRY was evaluated in PTPs and PUPs/MTPs. During clinical trials conducted in 153 adult/adolescent PTPs (defined as having ≥ 150 exposure days) and 51 pediatric PTPs (defined as having ≥ 50 exposure days) diagnosed with severe hemophilia A (FVIII $< 1\%$) (see [14 CLINICAL TRIALS](#)), one case of transient low titer inhibitor development (peak titer: 1.0 BU/mL) occurred in a 13 year old PTP after 549 EDs. The Factor VIII recovery was normal (2.7 IU/dL per IU/kg).

In the clinical trial that enrolled PUPs and MTPs (defined as having had ≤ 3 EDs to a factor VIII product at the time of enrollment), Factor VIII inhibitors were detected in 23 of 42 (54.8%) patients with a median (range) of 9 (4 – 42) EDs at the time of the first positive inhibitor test. Of these, 6 patients had low titer inhibitors (≤ 5.0 BU) and 17 patients (40.5%) had high titer inhibitors (> 5.0 BU). In patients who developed high titer inhibitors, high-risk mutations for inhibitor development were identified in 12 of 14 (85.7%) patients with available FVIII mutation data.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No interactions between human coagulation Factor VIII products and other medicinal products have been reported.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

KOVALTRY (Antihemophilic Factor [Recombinant]) provides a means of temporarily replacing the missing clotting Factor VIII for effective hemostasis. See [1 INDICATIONS](#).

10.2 Pharmacodynamics

The activated partial thromboplastin time (aPTT) is prolonged in people with hemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of Factor VIII. Treatment with rFVIII normalizes the aPTT to that achieved with plasma-derived factor VIII.

10.3 Pharmacokinetics

The pharmacokinetic (PK) properties of KOVALTRY were investigated in one clinical trial with adult/adolescent PTPs (12-62 years of age) with severe hemophilia A. At the beginning of the study, PK was evaluated in 26 subjects following injection of 50 IU/kg of KOVALTRY or KOGENATE FS with at least 3 days washout. After 6-12 months routine prophylactic treatment of KOVALTRY, 19 out of 26 subjects had a second PK evaluation following injection of 50 IU/kg of KOVALTRY. Serial blood samples were collected over 48 hours. Both KOVALTRY and KOGENATE FS were released using chromogenic assay for this PK evaluation.

Table 6: Pharmacokinetic parameters [Geometric mean (%CV)] in adults and adolescents (12-62 years of age) for KOVALTRY compared to KOGENATE FS using one-stage assay at beginning of the study

	KOGENATE FS (N=26)	KOVALTRY (N=26)	The geometric mean ratio (95%CI)
C_{max} (IU/dL)	101.3 (19.9)	96.6 (18.8)	0.95 (0.86 – 1.05)
AUC (IU*h/dL)	1175.7 (39.2)	1397.5 (37.9)	1.19 (1.12 – 1.27)
t_{1/2} (h)	12.2 (24.9)	13.4 (26.0)	1.10 (1.02 – 1.17)
CL (dL/h/kg)	0.043 (39.2)	0.036 (37.9)	0.84 (0.79 – 0.90)
MRT (h)	16.1 (27.6)	18.4 (28.6)	1.14 (1.07-1.21)
V_{ss} (dL/kg)	0.69 (27.7)	0.66 (21.8)	0.96 (0.87-1.06)

Table 7 - Pharmacokinetic parameters [Geometric mean (%CV)] in adults and adolescents (12-62 years of age) for KOVALTRY compared to KOGENATE FS using chromogenic assay at beginning of the study

	KOGENATE FS (N=26)	KOVALTRY (N=26)	The geometric mean ratio (95%CI)
C_{max} (IU/dL)	136.2 (23.8)	130.1 (23.0)	0.96 (0.85 – 1.08)
AUC (IU*h/dL)	1583.9 (39.9)	1889.2 (36.1)	1.19 (1.09 – 1.30)
t_{1/2} (h)	12.0 (28.2)	13.8 (28.0)	1.15 (1.06 – 1.24)
CL (dL/h/kg)	0.032 (39.9)	0.026 (36.1)	0.84 (0.77 – 0.91)
MRT (h)	16.5 (27.4)	19.3 (26.8)	1.17 (1.09 – 1.25)
V_{ss} (dL/kg)	0.52 (32.0)	0.51 (31.0)	0.98 (0.89 – 1.08)

Figure 1 - One-stage clotting assay: Concentration time profile of FVIII (IU/dL) following administration of 50 IU/kg KOVALTRY (BAY 81-8973) and KOGENATE FS – geometric means (SD) (PK analysis population LEOPOLD I Part A)

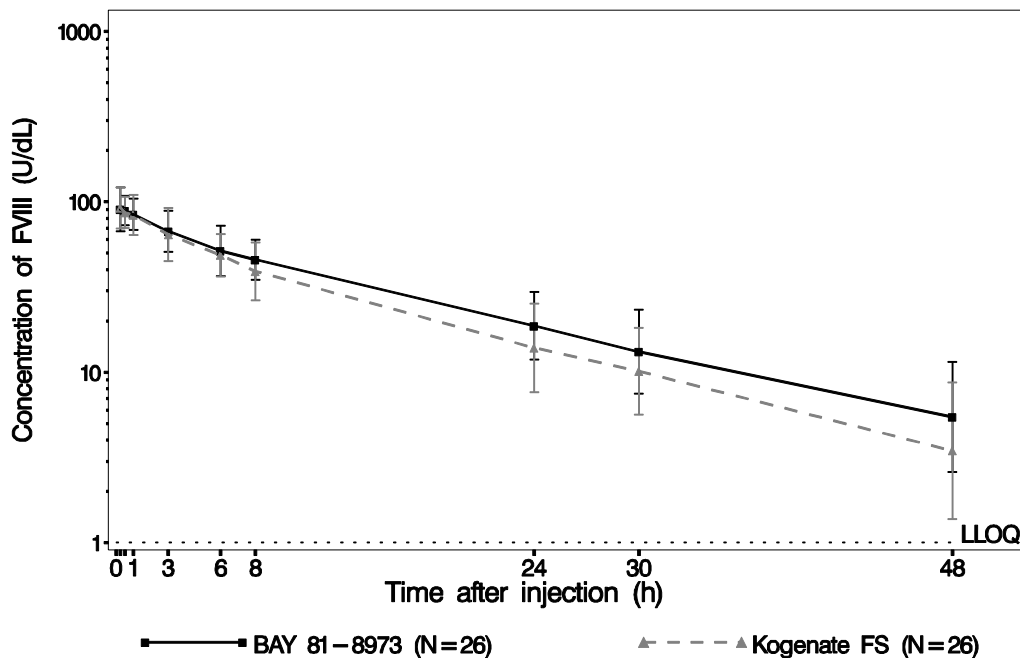


Figure 2 - Chromogenic assay: Concentration time profile of FVIII (IU/dL) following administration of 50 IU/kg KOVALTRY (BAY 81-8973) and KOGENATE FS – geometric means (SD) (PK analysis LEOPOLD I population Part A)

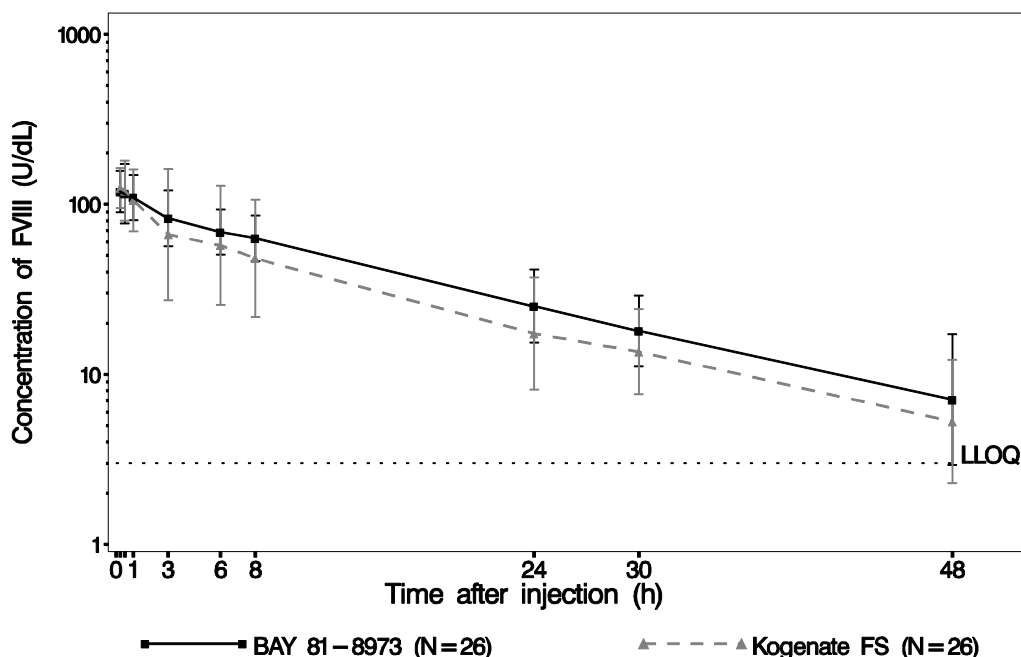


Table 8: Pharmacokinetic parameters [Geometric mean (%CV)] in adults and adolescents (12-62 years of age) for KOVALTRY at beginning of the study compared to post 6-12 months routine prophylactic treatment using one-stage assay

	At beginning of the study (N=19)	After 6-12 months routine prophylactic treatment of KOVALTRY (N=19)
C_{max} (IU/dL)	95.7 (13.5)	119.9 (22.0)
AUC (IU*h/dL)	1575.6 (33.9)	1725.2 (34.6)
t_{1/2} (h)	14.1 (27.7)	13.8 (27.4)

In an international field study involving 41 clinical laboratories, the performance of KOVALTRY in FVIII clotting activity (FVIII:C) assays was evaluated and compared to a marketed full length rFVIII product. Consistent results were determined for both products. The FVIII:C of KOVALTRY can be accurately measured in plasma with a one-stage coagulation assay as well as with a chromogenic assay using the routine methods of the laboratory.

Incremental Recovery

The analysis of all recorded *in vivo* recoveries (IVR) in adult/adolescent PTPs demonstrated a median rise of FVIII:C of >2 IU/dL per IU/kg body weight after administration of KOVALTRY (determined using both chromogenic substrate assay and one-stage coagulation assay) (see [14 CLINICAL TRIALS](#)).

Table 9: In vivo recovery results in adults and adolescents PTPs (12-65 years of age)

	LEOPOLD I Study	LEOPOLD II Study
Study participants	N=59	N=56
Chromogenic assay results Median (Q1; Q3), range	2.5 (2.1; 2.8), 0.2 – 4.6	2.1 (1.7; 2.4), 0.7 – 3.0
One-stage assay results Median (Range) (IU/dL per IU/kg)	2.2 (1.1; 3.1)	2.1 (1.2; 4.3)

Q1: 25% of subjects, Q3: 75% of subjects

Table 10: In vivo recovery results in Pediatric PTPs (<12 years of age)

LEOPOLD Kids Study				
	0 – <6 years		6 – 12 years	
	Start of study (N=24)	After 6 months of routine prophylactic treatment (N=23)	Start of study (N=25)	After 6 months of routine prophylactic treatment (N=25)
Chromogenic assay results Median (Range) (Q1; Q3) (IU/dL per IU/kg)	1.6 (0.7; 2.5) (1.3; 1.9)	1.8 (0.5; 3.1) (1.5; 2.0)	1.7 (0.6; 2.7) (1.4; 2.0)	1.8 (0.5; 2.8) (1.2; 2.1)

Special Populations and Conditions

Pediatrics (< 12 years of age)

Pharmacokinetic parameters calculated from 15 PTP subjects < 12 years of age are available for 5 subjects in age group 1 - < 6 years and 10 subjects in age group 6 - < 12 years as shown in [Table 11](#). Subjects received a dose of 50 IU/kg of KOVALTRY. Blood samples were obtained pre-injection and at 20-30 minutes, 4 hours, and 24 hours after the injection of KOVALTRY.

Table 11: PK parameters (Geometric mean (%CV)) for KOVALTRY in PTP children <12 years based on chromogenic assay

	PTPs 1 – <6 years N = 5	PTPs 6 – <12 years N = 10	PTPs Total N = 15
Parameter [unit]	Geom. mean (%CV)	Geom. mean (%CV)	Geom. mean (%CV)
AUC [IU*h/dL]	1334.3 (29.4) ^a	1155.4 (34.7)	1203.9 (32.8)
C _{max} [IU/dL]	74.2 (40.5)	79.8 (23.5)	77.9 (28.7)
t _{1/2} [h]	11.8 (27.0) ^a	11.9 (16.6)	11.9 (18.9)
CL [dL/h/kg]	0.04 (25.1) ^a	0.04 (34.8)	0.04 (32.2)
MRT _{IV} [h]	17.3 (24.9) ^a	17.6 (15.5)	17.5 (17.6)
V _{ss} [dL/kg]	0.64 (20.6) ^a	0.76 (28.6)	0.72 (27.1)

a: N=4 for PTPs 1 - < 6 years

Hepatic impairment

Dose adjustment for patients with hepatic impairment has not been studied in clinical trials.

Renal impairment

Dose adjustment for patients with renal impairment has not been studied in clinical trials.

Duration of Effect

The duration of effect is variable and dependent on the individual patient, the severity of the bleed and the clinical situation.

11 STORAGE, STABILITY AND DISPOSAL

KOVALTRY (Antihemophilic Factor [Recombinant]) should be stored under refrigeration (2°C-8°C). Do not use beyond the expiration date indicated on the vial. Storage of lyophilized powder at room temperature up to 25°C for 12 months, such as in home storage situations, may be done. If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 12 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once product is removed from refrigeration, it cannot be returned to the refrigerator. Freezing must be avoided. Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

After reconstitution, the product should be used immediately (within 3 hours).

12 SPECIAL HANDLING INSTRUCTIONS

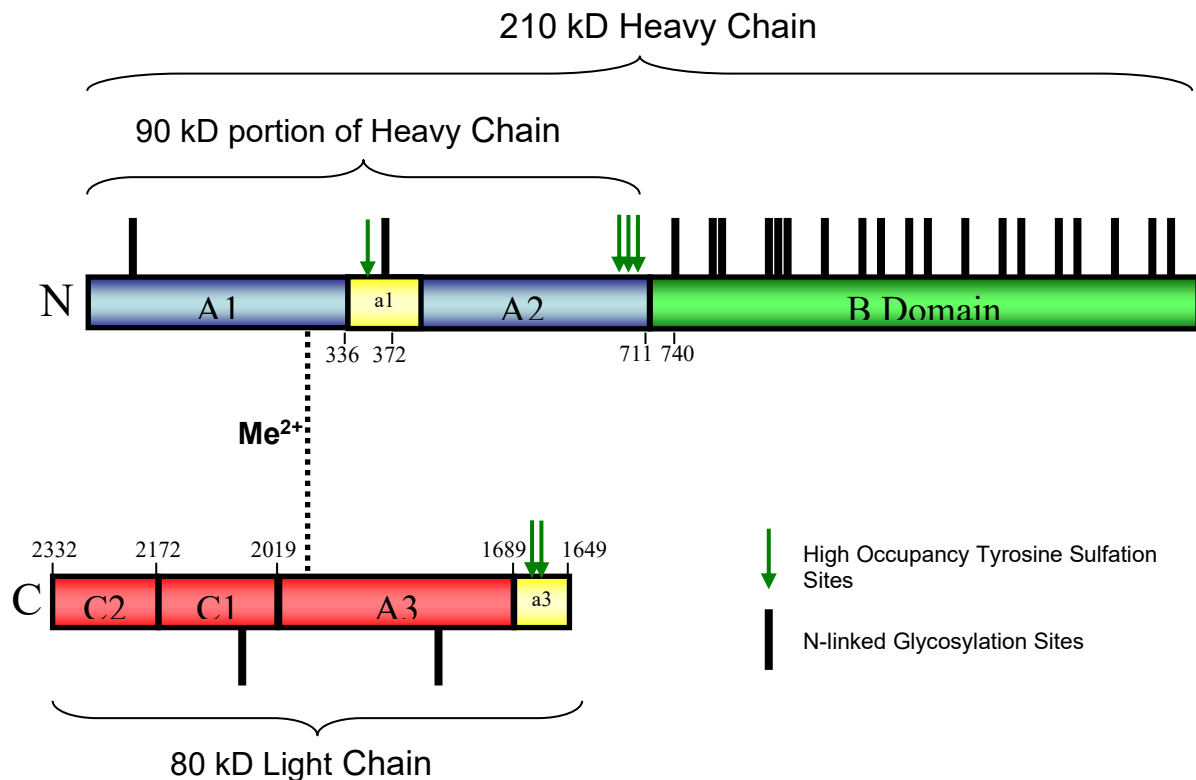
Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Antihemophilic Factor (Recombinant)
Chemical name:	Recombinant Human Coagulation Factor VIII
Molecular formula:	2332 amino acids
Molecular weight:	Approx. 330-360 kDa
Structural formula:	heavy chain C8241H12908N2264O2528S50 and light chain C3553H5408N956O1026S33



The glycoprotein is synthesized as a single chain 330-kD precursor with a domain structure of A1-A2-B-A3-C1-C2 subunits. Proteolytic processing at the B-A3 (between Arg 1648 and Glu 1649) junction yields A1-A2-B heavy chain and A3-C1-C2 light chains to form a large heterodimeric structure linked by a divalent cation bridge. Multiple N-linked and O-linked glycans are present on the structure, predominantly within the B-domain. The A1 and A3-C1-C2 domains each have two occupied N-linked sites. Additionally, there are six highly occupied tyrosine sulfation sites and one site in the A2 domain with very low occupancy.

Physicochemical properties: KOVALTRY is a water soluble glycosylated protein that is unstable in final form in the absence of excipients. In final form the protein is stabilized in solution with excipients and lyophilized.

Product Characteristics

KOVALTRY is a recombinant, full length, unmodified, Factor VIII concentrate that is sterile, stable over the shelf life of the product, purified, and nonpyrogenic. It is produced by genetically engineered Baby Hamster Kidney (BHK) cells into which the human Factor VIII gene has been introduced. KOVALTRY has the identical FVIII amino acid sequence, the same molecular formula, proteolytic processing and similar post translational modifications (glycosylation and sulfation) as the licensed KOGENATE FS. Oligosaccharide characterization of the final product has shown superior glycosylation, better branching, and sialylation capping of terminal galactose residues. KOVALTRY has the same biological activity as Factor VIII derived from human plasma. Human- and animal-derived raw materials are not used in the cell culture, purification, and formulation processes.

The BHK cell line has been modified with the human heat shock protein 70 (HSP70) to enhance proper protein folding and resistance to apoptosis. The cell culture process employs a continuous perfusion process and is followed by an automated continuous cell separation process.

The potency (IU) of the drug product is determined using the chromogenic assay. This potency assignment employs a Factor VIII concentrate standard that is referenced to a WHO International Standard for Factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

Viral Inactivation

To achieve a high virological safety level, the manufacturing process incorporates dedicated viral clearance steps which include a detergent virus inactivation step, and a 20-nm filtration step for removal of viruses (including small and non-enveloped) and potential protein aggregates. The purification process includes methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, and other chromatographic steps, designed to purify recombinant Factor VIII and remove process- and product-related impurities.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The safety, efficacy and pharmacokinetics of KOVALTRY were evaluated in three open-label, multicenter clinical trials (Table 12). A total of 204 male previously treated patients (PTPs) with severe hemophilia A ($\leq 1\%$ FVIII activity) have been included in the trial program. There were 153 subjects aged ≥ 12 years old, and 136 of them had ≥ 50 exposure days (EDs) in the clinical trials. The median number of exposure days of 142 subjects participating in the safety and efficacy part of the studies was 159 (range: 8 to 355). There were 51 PTPs aged ≤ 12 years old, and 50 of them had ≥ 50 EDs in the main clinical trial. The median number of exposure days was 73 (range: 37 to 103). A total of 43 male previously untreated patients (PUPs) / minimally treated patients (MTPs) < 6 years old with severe hemophilia A ($\leq 1\%$ FVIII activity) have been exposed in the main trial program and accumulated a median of 46 EDs (range 1 to 55 EDs).

Of the 94 subjects aged ≤ 12 years old treated in LEOPOLD Kids main studies, 82 subjects (46 subjects from Part A, 36 subjects from Part B) continued in the extension study, of which 67 subjects received KOVALTRY for routine prophylaxis treatment. The median time in the extension study was 3.1 years (range 0.3 to 6.4 years) for the 82 subjects and 3.8 years (range 0.5 to 6.4 years) for the 67 subjects who received routine prophylaxis treatment. The median total time for the 82 subjects in the entire study (main and extension) was 3.8 years (range 0.8 to 6.7 years), and the majority of subjects (76 of 82, 92.7%) accumulated at least 100 cumulative EDs.

Table 12: Summary of Patient Demographics and Trial Design

Study #	Trial Design	Dosage of KOVALTRY	# of subjects	Median (range) age (year)
LEOPOLD I	Open-label, multicenter	Part A: PK 50 IU/kg (compared to Kogenate FS 50 IU/kg)	26 PTPs	28.5 (12–61)
		Part B: prophylaxis (regimen at investigator’s discretion): 20-50 IU/kg 2-3 x/ week for 12 months, with 6 months per potency (CS/EP and CS/ADJ) assignment	62 PTPs	30.0 (12–61)
		Dosing frequency 2x/week	18 PTPs	40 (12-61)
		Dosing frequency 3x/week	44 PTPs	29 (12-60)
		Part C: peri-operation: according to standard practice for the use of Kogenate FS.	5 PTPs	37.0 (28-38)
Extension: Prophylaxis / on-demand / peri-operation	55 PTPs	31.0 (12-61)		
LEOPOLD II	Open-label, multicenter, randomized	Prophylaxis group by randomization:	28 PTPs	30.0 (14–53)
		Dosing frequency 2x/week low dose (20 – 30 IU/kg)	31 PTPs	27.0 (14–54)
		Dosing frequency 3x/week high dose (30 – 40 IU/kg)	21 PTPs	28.0 (14–59)
		On-demand group (randomized): dosing according to treatment recommendation for Kogenate FS		
12 months in total, with 6 months per potency (CS/EP and CS/ADJ) assignment				
LEOPOLD KIDS	Open-label, multicenter	Part A: 25 – 50 IU/kg prophylaxis at least 2x/week (regimen assigned by investigator), treatment of breakthrough bleeds and prevention of bleeds during surgical procedures; approximately 6 months and at least 50 EDs.	51 PTPs	6.0 (1–11)
		Optional PK measurements (patients to receive exact dose of 50 IU/kg)	15 PTPs	
		Part B: 15 – 50 IU/kg (minimum 250IU); prophylaxis at least 1x/week (regimen assigned by investigator), treatment of breakthrough bleeds and prevention of bleeds during surgical procedures; 50 EDs.	43 PUPs / MTPs	0.9 (0.1-5.6)
		Extension (82 subjects from LEOPOLD Kids Part A and Part B); at least 100 EDs	46 PTPs from Part A; 36 PUPs / MTPs from Part B	7.00 (2.0-12.0); 2 (1.0 – 4.0)

*CS/EP: Treatment with labeled potency (and dose assignment) based on the chromogenic substrate assay according to European Pharmacopoeia

*CS/ADJ: Treatment with label-adjusted potency (and dose assignment) mimicking one-stage assay using a pre-defined factor.

14.2 Study Results

Routine Prophylaxis

Adolescents and Adults

The median Annualized Bleeding Rate (ABR) for the ITT population in LEOPOLD I was 1.0 bleeds/year. In LEOPOLD II, comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis regimen demonstrated a statistically significant difference (ANOVA; $p < 0.0001$) in the median ABR in subjects receiving on-demand therapy (60 bleeds per year) as compared to subjects receiving prophylaxis regimen (2 bleeds per year). In LEOPOLD I Part B or LEOPOLD I Extension, no remarkable difference was seen in the ABRs between prophylaxis treatment 2 times per week or 3 times per week, supporting the practice of a clinically guided selection of dose according to patient requirements for effective prophylaxis treatment.

Table 13: Annualized Bleeding Rate (ABR) in Adolescent and Adult Patients in LEOPOLD I and LEOPOLD II Studies

	LEOPOLD I Study		LEOPOLD II Study	
	First Year (N=62)	Second Year (N=55)	Low dose, 2 x/week (N=28)	High dose, 3x/week (N=31)
Median Overall ABR (Range)	1.03 (0.0, 26.1)	1.97 (0.0, 20.1)	4.02 (0.0, 33.1)	1.97 (0.0, 25.9)
Median Spontaneous ABR (Range)	1.01 (0.0, 16.7)	0.98 (0.0, 13.5)	2.01 (0.0, 33.1)	0.0 (0.0, 20.6)
Median Traumatic ABR (Range)	0.0 (0.0, 24.1)	0.0 (0.0, 17.0)	0.0 (0.0, 6.0)	0.98 (0.0, 14.9)
Median Joint ABR (Range)	1.04 (0.0, 25.1)	1.02 (0.0, 14.0)	2.52 (0.0, 32.1)	1.01 (0.0, 24.9)

Children 12 Years of Age and Younger

In Part A of the LEOPOLD KIDS study, a total of 51 previous treated patients (PTPs) aged ≤ 12 years old received six months of prophylactic KOVALTRY treatment. The annualized bleed rate (ABR) is presented in [Table 14](#).

Table 14: Annualized Bleeding Rate (ABR) in Children ≤ 12 years old in Part A of the LEOPOLD KIDS Study

	LEOPOLD KIDS Study (Part A)		
	PTPs 0-6 years (N=25)	PTPs 6-12 years (N=26)	PTPs (Total)
Median Overall ABR (Range)	2.03 (0.0, 18.1)	0.93 (0.0, 17.7)	1.90 (0.0, 18.1)
Median Spontaneous ABR (Range)	0.0 (0.0, 6.0)	0.0 (0.0, 12.0)	0.0 (0.0, 12.0)
Median Traumatic ABR (Range)	0.0 (0.0, 4.1)	0.0 (0.0, 17.7)	0.0 (0.0, 17.7)
Median Joint ABR (Range)	0.0 (0.0, 4.1)	0.0 (0.0, 15.8)	0.0 (0.0, 15.8)

In Part B of the LEOPOLD KIDS study, a total of 43 PUPs/MTPs aged <6 years old received prophylactic KOVALTRY treatment at least once weekly. The median overall Annualized Bleeding Rate (ABR) was 4.7 (range 0 – 45).

For the 20 subjects with no Factor VIII inhibitor, the median overall ABR within 48 hours after prophylactic infusion during the prophylaxis treatment period was 0.0 (range 0 - 6).

During the extension study, the majority of subjects (61 of 67; 91%) received KOVALTRY prophylaxis at a dosing frequency of at least 2 times per week. The median dose per prophylactic infusion was 34 IU/kg (range 16 – 57 IU/kg). The median (range) ABR for total bleeds occurring within 48 h after a prophylaxis infusion was 0.7 (0 to 12). Median (range) ABR independent of time of infusion was 1.9 (0 to 24).

Control of Bleeding Episodes

Adolescents and Adults

A total of 1887 bleeding episodes in 108 subjects were treated with KOVALTRY. The majority of the bleeding episodes were spontaneous, localized in joints, and mild to moderate in severity (see [Table 15](#)). The median consumption of KOVALTRY for the treatment of breakthrough bleeds was 28.6 IU/kg/injection (range 13-54 IU/kg) and 28 IU/kg (range 11-49 IU/kg) in the LEOPOLD I and LEOPOLD II main studies, respectively.

The majority of bleeding episodes (87.6% in LEOPOLD I; 96.2% and 95.3% in prophylaxis and on-demand arms, respectively in LEOPOLD II) were resolved with one or two infusions of KOVALTRY.

Table 15: Control and Prevention of Bleeding Episodes in Adolescents and Adults Treated with KOVALTRY

Characteristics of Bleeding Episodes	LEOPOLD I		LEOPOLD II	
	Prophylaxis Main Study N=62	Prophylaxis Extension N=55	Prophylaxis N=59	On-demand N=21
Patients with bleeds				
Total number of bleeds	236	154	293	1204
Spontaneous	63.5%	52.7%	73.9%	78.5%
Mild/moderate	89.2%	84.9%	88.8%	91.3%
Joint bleeds	79.3%	77.9%	87%	77.2%
Number of infusions/bleed treatment (median; range)	1.0 (0; 48)		1.0 (0;7)	1.0 (0; 20)
% of bleeds treated with ≤ 2 infusions	87.6%		96.2%	95.3%
Median dose/infusion (range)	31.6 IU/kg (14-67 IU/kg)		28 IU/kg (11-49 IU/kg) 29.4 IU/kg (19-49 IU/kg)	22.0 IU/kg (11-35 IU/kg)

Children 12 Years of Age and Younger

A total of 97 bleeding episodes in 28 previously treated subjects were treated with KOVALTRY in the LEOPOLD Kids Part A main study. The majority (96.8%) of the bleeds were mild to moderate in severity. Fifty nine (72.8%) bleeds were trauma related. During the 6 month treatment period, the median consumption of KOVALTRY for the treatment of breakthrough bleeds was 36.94 IU/kg/injection (range 20.8–71.6 IU/kg).

The majority of bleeds (89.7%) were successfully treated with one to two infusions (92.4% in patients from 0 to 6 years of age and 86.7% of patients 6 to 12 years of age).

Table 16: Control and Prevention of Bleeding Episodes in Previously Treated Children Treated with KOVALTRY

	LEOPOLD Kids Part A		
	PTPs 0 to <6 years (N=25)	PTPs 6 to 12 years (N=26)	PTPs (Total)
Location of bleeds n/total	Skin/mucosa: 28/52 (53.8%) Joint: 10/52 (19.2%)	Skin/mucosa: 17/45 (37.8%) Joint: 22/45 (48.9%)	45/97 (46.4%) 32/97 (33.0%)
Bleed severity, n (%)	Mild: 33 (63.5%) Moderate: 17 (32.7%) Severe: 2 (3.8%)	Mild: 17 (37.8%) Moderate: 27 (60.0%) Severe: 1 (2.2%)	50 (51.4%) 44 (45.4%) 3 (3.1%)
Type of bleeds	Spontaneous: 18.2% Trauma: 81.8%	Spontaneous: 32.4% Trauma: 62.2% Unspecified: 5.4%	20 (24.7%) 59 (72.8%) 2 (2.5%)
Number of infusions/bleed treatment (median; range)	1.0 (0; 9)	1.0 (0;8)	1.0 (0;9)
Patient assessment as 'excellent' or 'good'	97.8%	81.0%	90.1%
Dose/infusion (range)	38.7 IU/kg (20.8–71.6 IU/kg)	32.4 IU/kg (21.7–50.0 IU/kg)	36.9 IU/kg (20.8–71.6 IU/kg)

A total of 105 out of 184 bleeding episodes in 37 previously untreated and minimally treated subjects were treated with KOVALTRY in the LEOPOLD Kids Part B main study. The majority (102/105, 97.1%) of the bleeds were mild to moderate in severity. Sixty-two (62/105, 59.0%) bleeds were trauma related.

Of the bleeds that were treated (105/184), the majority (82/105, 78.1%) were successfully treated with one to two infusions.

Table 17: Control and Prevention of Bleeding Episode in Previously Untreated/Minimally Treated Children Treated with KOVALTRY

	LEOPOLD Kids Part B		
	PUPs (N=37)	MTPs (N=6)	Total
Location of bleeds n/total	Skin/mucosa: 48/96 (50.0%) Muscle: 22/96 (22.9%) Joint: 16/96 (16.7%) Internal: 2/96 (2.1%) Other: 12/96 (12.5%)	Skin/mucosa: 2/9 (22.2%) Muscle: 1/9 (11.1%) Joint: 5/9 (55.6%) Internal: 0 Other: 1/9 (11.1%)	Skin/mucosa: 50/105 (47.6%) Muscle: 23/105 (21.9%) Joint: 21/105 (20.0%) Internal: 2/105 (1.9%) Other: 13/105 (12.4%)
Bleed severity, n (%)	Mild: 37/96 (38.5%) Moderate: 56/96 (58.3%) Severe: 3/96 (3.1%)	Mild: 5/9 (55.6%) Moderate: 4/9 (44.4%) Severe: 0	Mild: 42/105 (40.0%) Moderate: 60/105 (57.1%) Severe: 3/105 (2.9%)
Type of bleeds (treated bleeds), n/total (%)	Spontaneous: 33/96 (34.4%) Trauma: 59/96 (61.5%) Other: 4/96 (4.2%)	Spontaneous: 6/9 (66.7%) Trauma: 3/9 (33.3%)	Spontaneous: 39/105 (37.1%) Trauma: 62/105 (59.0%) Other: 4/105 (3.8%)
Number of infusions/bleed treatment (median; range)	1.0 (1; 118)	2.0 (1; 8)	1.0 (1; 118)
Patient assessment as 'excellent' or 'good', n/total (%)	74/96 (77.1%)	9/9 (100%)	83/105 (79.0%)
Dose/infusion (range)	41.0 IU/kg (21–112 IU/kg)	37.9 IU/kg (33–42 IU/kg)	40.5 IU/kg (21–112 IU/kg)

Amongst the 67 subjects who received prophylaxis treatment in the LEOPOLD Kids extension study, a total of 472 bleeds were treated with KOVALTRY, requiring 1-2 infusions for the majority of bleeds (394 of 472; 83.5%), and response to treatment was good or excellent in most (415 of 472; 87.9%) of the cases.

Peri-operative Management

A total of 11 major surgeries were performed in 9 previously treated subjects (adults and children) with severe hemophilia A. Five of the 11 major surgeries were orthopedic procedures, including joint replacement. All subjects received KOVALTRY as bolus injections. In the adolescents and adults subjects, the initial KOVALTRY doses administered ranged between 3000–5000 IU (nominal dose). In a single subject younger than 12 years of age who underwent a major surgery, the total initial KOVALTRY dose administered was 2500 IU (108.7 IU/kg).

Hemostatic control was assessed by surgeons as “good” or “excellent”.

Non-inferiority testing of CS/EP versus CS/ADJ Potency

Data from LEOPOLD I Part B (excluding data from the extension phase) and LEOPOLD II (prophylaxis group) were combined to test the non-inferiority of prophylactic treatment with KOVALTRY dose

determined by chromogenic substrate per European Pharmacopoeia (CS/EP) versus KOVALTRY dose determined by the label-adjusted potency mimicking the one-stage assay (CS/ADJ).

Despite an approximately 20% lower actual FVIII dose, the efficacy of prophylaxis treatment with KOVALTRY in the prevention of bleeds using the potency determined by CS/EP mode was statistically proven as non-inferior to treatment using the potency determined by CS/ADJ mode. The median difference between ‘ABR on prophylaxis treatment with CS/ADJ’ compared to ‘ABR on prophylaxis with CS/EP’ was 0.00 bleeds/year for LEOPOLD I, LEOPOLD II and for the pool.

The non-inferiority of CS/EP versus CS/ADJ based dosing was also proven for the treatment of bleeds in the on-demand group, in relation to the number of bleeds treated with up to 2 injections (LEOPOLD II). Non-inferiority testing resulted in $p < 0.0001$ (exact permutation test for paired samples), ie, the non-inferiority of CS/EP to CS/ADJ was demonstrated.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Toxicology studies of KOVALTRY (see [Table 18](#)) included single and repeated (5-day) intravenous administration toxicology studies in male rats and rabbits, with recovery groups and supportive toxicokinetics in the repeat-dose studies. In addition, the genotoxicity of KOVALTRY was assessed in vitro. This mutagenicity testing was conducted based on an agency concern that human heat-shock protein 70 (HSP70) in the production cell line may result in a mutagenic concern.

Local tolerability was assessed as part of the acute and repeat dose toxicity studies.

Comparative antigenicity studies between KOVALTRY and the currently marketed product KOGENATE FS were performed. Bayer selected the hemophilia A mouse model for this purpose. Anti-FVIII antibody formation was also examined in the pivotal repeat dose toxicity studies in rats and rabbits as part of an immunogenicity plan.

Table 18: Toxicology Program

Type of Study/ Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Administration	Compound administered	Doses	Key Findings
Single-Dose Toxicity					
Single dose toxicity (+ 2-week recovery)	Rat, Sprague-Dawley, 6/M / group	IV	KOVALTRY (2 lots)	0, 400, 4000 IU/kg	KOVALTRY was well tolerated in male rats and rabbits and no treatment-related adverse
	Recovery, 4/M / group	IV	KOVALTRY A(2 lots)	0, 4000 IU/kg	

Type of Study/ Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Admini stration	Compound administered	Doses	Key Findings
	Rabbit, New Zealand White, 3/M/ group Recovery, 3/M/ group	IV IV	KOVALTRY (2 lots) KOVALTRY (2 lots)	0, 400, 4000 IU/kg 0, 4000 IU/kg	effects were observed up to the highest dose tested. The NOAEL is >4000 IU/kg; this is up to 80 to 200 times the clinical dose of 20 to 50 IU/kg. Locally at the injection sites KOVALTRY was well tolerated.
Repeat-Dose Toxicity					
5-day systemic toxicity (GLP) (+ 4-week recovery, TK)	Rat, Sprague-Dawley; 10/M / group	IV	KOVALTRY	0, 40, 120, 400 IU/kg	KOVALTRY was well tolerated in rats and rabbits and no treatment-related adverse effects were seen. The NOAEL after repeated administration is >400 IU/kg. Locally at the injection sites KOVALTRY was well tolerated.
	Recovery; 5/M / group	IV	KOVALTRY	0, 400 IU/kg	
	Rabbit, New Zealand White; 6/M / group	IV	KOVALTRY	0, 40, 120, 400 IU/kg	
	Recovery; 3/M / group	IV	KOVALTRY	0, 400 IU/kg	
Genotoxicity					
In vitro Mutagenicity (Mouse lymphoma assay, GLP)	L5178Y cell line	<i>In vitro</i>	KOVALTRY	pulse treatment: 25 % (1.25 mL per 5 mL culture) continuous treatment: 4 % (0.4 mL per 10 mL culture)	KOVALTRY has been shown to be non-mutagenic and non-clastogenic in mammalian cells in the mouse lymphoma assay.

Type of Study/ Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Admini stration	Compound administered	Doses	Key Findings
Other toxicity studies					
Immunogenicity (non GLP)	Mice, Hemophilia A; 10/M / group	IV	KOVALTRY KOGENATE FS	40 or 200 IU/kg	KOVALTRY treatment did not result in a statistically different formation of total and neutralizing antibody titres when compared with KOGENATE FS.

GLP = good laboratory practice (regulations); IV=intravenous; M =male; NOAEL=No Adverse Effect Level;
TK=including toxicokinetics

The nonclinical safety program did not identify any concerns for humans based on safety pharmacology, acute toxicity, repeated-dose toxicity and genotoxicity studies.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KOVALTRY®

Antihemophilic Factor (Recombinant)

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

Serious Warnings and Precautions

- The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A

What is KOVALTRY used for?

- KOVALTRY is used for treatment and prevention (prophylaxis) of bleeding in patients with hemophilia A (congenital factor VIII deficiency).
- It is also used for prophylaxis treatment of children with hemophilia A to reduce the occurrence of spontaneous bleeding episodes.
- This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

How does KOVALTRY work?

KOVALTRY is clotting Factor VIII. It is very similar to the Factor VIII that occurs naturally in human blood. In patients with hemophilia A, who do not have enough natural Factor VIII in their blood, KOVALTRY gives them additional Factor VIII to help prevent and/or control bleeding. KOVALTRY is given directly into the blood through an injection in a vein. KOVALTRY is prepared by recombinant technology without addition of any human- or animal-derived components in the manufacturing process.

What are the ingredients in KOVALTRY?

Medicinal ingredients: Antihemophilic Factor (Recombinant)

Non-medicinal ingredients: Calcium chloride, Histidine, Glycine, Polysorbate 80, Sodium chloride, Sucrose

KOVALTRY comes in the following dosage forms:

KOVALTRY 250 IU:

The vial with powder contains 250 IU (International Units) of Antihemophilic Factor (Recombinant). After reconstitution with the water for injection (2.5 mL), each vial contains octocog alfa 100 IU/mL.

KOVALTRY 500 IU:

The vial with powder contains 500 IU (International Units) of Antihemophilic Factor (Recombinant). After reconstitution with the water for injection (2.5 mL), each vial contains octocog alfa 200 IU/mL.

KOVALTRY 1000 IU:

The vial with powder contains 1000 IU (International Units) of Antihemophilic Factor (Recombinant). After reconstitution with the water for injection (2.5 mL), each vial contains octocog alfa 400 IU/mL.

KOVALTRY 2000 IU:

The vial with powder contains 2000 IU (International Units) of Antihemophilic Factor (Recombinant). After reconstitution with the water for injection (5 mL), each vial contains octocog alfa 400 IU/ mL.

KOVALTRY 3000 IU:

The vial with powder contains 3000 IU (International Units) of Antihemophilic Factor (Recombinant). After reconstitution with the water for injection (5 mL), each vial contains octocog alfa 600 IU/ mL.

Do not use KOVALTRY if:

- If you are allergic (hypersensitive) to octocog alfa, or to any of the other ingredients of KOVALTRY
- If you have had allergic reactions to mouse or hamster protein.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KOVALTRY. Talk about any health conditions or problems you may have, including if you:

- are allergic to mouse or hamster protein

Other warnings you should know about:

If you experience tightness in the chest, feel dizzy, sick or faint, or experience dizziness upon standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to KOVALTRY. If this occurs, **stop administration of the product** immediately and seek medical advice.

Your doctor may carry out tests to ensure that your current dose of KOVALTRY provides adequate Factor VIII levels.

- If your bleeding is not being controlled with your usual dose of KOVALTRY, consult your doctor immediately. You may have developed Factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the Factor VIII you are using, and makes it less effective to prevent and control bleeding.
- If you have previously developed a Factor VIII inhibitor and you switch Factor VIII products, you may be at risk of your inhibitor coming back.

When frequent injections are required, your healthcare professional may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. This device may result in an infection. Inform your healthcare provider if you have a catheter-related infection.

Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.

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

The following may interact with KOVALTRY:


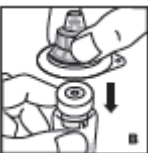

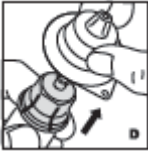


No interactions with other medicines are known. However, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

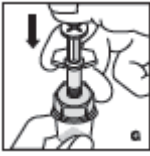




How to take KOVALTRY:

- KOVALTRY is intended for intravenous administration only and must be administered within 3 hours after reconstitution (see below).

You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (Vial Adapter, pre-filled syringe containing diluent and administration set) for reconstitution and administration that are provided with each carton of KOVALTRY. If a device package is opened or damaged, do not use this medical device. If these devices cannot be used, please contact your healthcare provider. If you have any questions about KOVALTRY contact Bayer at 1-800-265-7382 or canada.medinfo@bayer.com,

- KOVALTRY must **not** be mixed with other infusion solutions. Follow the directions given by your doctor closely and use the instructions below as a guide:

<p>1. Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C.</p>	
<p>2. Remove protective cap from the vial (A). Aseptically cleanse the rubber stopper with alcohol, being careful not to handle the rubber stopper.</p>	
<p>3. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.</p>	
<p>4. Holding the syringe by the barrel, snap the syringe cap off the tip (C). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.</p>	
<p>5. Now remove and discard the adapter plastic housing (D).</p>	
<p>6. Attach the prefilled syringe to the vial adapter thread by turning clockwise (E).</p>	
<p>7. Remove the clear plastic plunger rod from the carton. Grasp the plunger rod by the top plate. Avoid touching the sides and threads of the plunger rod. Attach the plunger rod by turning it clockwise into the threaded rubber stopper of the prefilled syringe (F).</p>	

<p>8. Inject the diluent slowly by pushing down on the plunger rod (G).</p>	
<p>9. Swirl vial gently until all powder on all sides of the vial is dissolved (H). Do not shake vial. Be sure that all powder is completely dissolved. Do not use if solution contains visible particles or is cloudy.</p>	
<p>10. Push down on the plunger to push all air back into the vial. Then while holding the plunger down, turn the vial with syringe upside-down (invert) so the vial is now above the syringe (I).</p>	
<p>11. Withdraw all the solution into the syringe by pulling the plunger rod back slowly and smoothly (J). Tilt the vial to the side and back to make sure all the solution has been drawn toward the large opening in the rubber stopper and into the syringe. Remove as much air as possible before removing the syringe from the vial by slowly and carefully pushing the air back into the vial.</p>	
<p>12. Detach the syringe with plunger rod from the vial adapter by turning counter-clockwise. Attach the syringe to the administration set provided and inject intravenously (K). NOTE: follow instructions for administration set provided.</p>	

If receiving more than one vial, reconstitute each concentrate vial as described above with the diluent syringe provided. To combine two or more doses, use a larger plastic syringe (not provided) and administer as usual.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Usual dose:

Treatment of bleeding

How much KOVALTRY you should use and how often you should use it depends on many factors such as your weight, the severity of your hemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the Factor VIII level that is needed.

Your doctor will calculate the dose of KOVALTRY and how frequently you should use it to get the necessary level of Factor VIII activity in your blood. He/she should always adjust the amount of KOVALTRY to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding

If you are using KOVALTRY to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. For an adult or adolescent (> 12 years of age) this will usually be in the range of 20 to 40 IU of KOVALTRY per kg of body weight, given 2-3 times per week. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

For children ≤ 12 years old, the recommended dose for routine prophylaxis is 20 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements.

Laboratory tests

It is strongly recommended that appropriate laboratory tests be performed on your plasma at suitable intervals to ensure that adequate Factor VIII levels have been reached and are maintained. For major surgery in particular, close monitoring of the treatment by means of coagulation analysis must be carried out.

If bleeding is not controlled

If the Factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after adequate dose, you may have developed Factor VIII inhibitors. This must be checked by an experienced doctor.

If you feel the effect of KOVALTRY is too strong or too weak, talk to your doctor.

Patients with inhibitors

If you have been told by your doctor that you have developed Factor VIII inhibitors you may need to use a larger amount of KOVALTRY to control bleeding.

Do not increase your dose of KOVALTRY you use to control your bleeding without consulting your doctor.

Speed of administration

KOVALTRY should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

Duration of treatment

Your doctor will tell you, how often and at what intervals KOVALTRY is to be administered.

Usually, replacement therapy with KOVALTRY is a life-time treatment.

Overdose:

No symptoms of overdose with recombinant coagulation Factor VIII have been reported.

If you think you, or a person you are caring for, have taken too much KOVALTRY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose.

Do not stop using KOVALTRY without consulting your doctor.

What are possible side effects from using KOVALTRY?

These are not all the possible side effects you may feel when taking KOVALTRY. If you experience any side effects not listed here, contact your healthcare professional. Please also see Product Monograph Part I: [7 WARNINGS AND PRECAUTIONS](#).

Common: may affect more than 1% and less than 10% of users

- stomach pain
- stomach discomfort
- indigestion
- fever
- local reactions where you injected the medication
- headache
- dizziness
- trouble falling asleep
- hives
- itchy skin
- rash

Uncommon: may affect more than 0.1% and less than 1% of users

- lymph nodes enlarged
- heart palpitations
- rapid heartbeat
- chest discomfort
- hypersensitivity reactions including severe sudden allergic reaction (anaphylactic shock, e.g. tightness of the chest/general feeling of being unwell, dizziness and nausea and mildly reduced blood pressure, which may make you feel faint upon standing)
- dysgeusia (odd taste)
- flushing (redness of the face)
- inhibitor (antibodies)
- allergic dermatitis

In addition to the side effects listed above, for children not previously treated or minimally treated (less than 3 days of treatment) with Factor VIII medicines:

Very common: may affect more than 10% of users

- inhibitor (antibodies)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Lack of effect		✓	
UNCOMMON			
Hypersensitivity reactions including severe sudden allergic reaction (anaphylactic shock, e.g. tightness of the chest/general feeling of being unwell, hives, dizziness and nausea and mildly reduced blood pressure, which may make you feel faint upon standing)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Do not use this medicine after the expiry date stated on the labels and cartons

Store in a refrigerator (2°C - 8°C). **Do not** freeze. Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

You may store the product when kept in its outer carton at room temperature (up to 25°C) for a single period of up to 12 months. Once the product is removed from refrigeration, it cannot be returned to the refrigerator.

The reconstituted solution should be used immediately (within 3 hours). This product is for single use only. Any unused solution must be discarded.

Do not use KOVALTRY if you notice any particles or the solution is cloudy.

Keep out of reach and sight of children.

If you want more information about KOVALTRY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>; the manufacturer's website <http://www.bayer.ca>, or by calling Bayer Medical Information at 1800265-7382 or canada.medinfo@bayer.com.

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Last Revised: Mar 7, 2023

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