PRODUCT MONOGRAPH

PrKOVALTRY®

Antihemophilic Factor (Recombinant)

Supplied with BIO-SET
Needle-less Reconstitution Set

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

Coagulation Factor FVIII

Manufactured by: Bayer Inc.
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TABLE OF CONTENTS

[Pr]KOVALTRY®

Antihemophilic Factor (Recombinant)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	Lyophilized powder for injection 250, 500, 1000, 2000, 3000 IU/vial	Sucrose Histidine Glycine Sodium chloride Calcium chloride Polysorbate 80 *For a complete listing* **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

DESCRIPTION

KOVALTRY (Antihemophilic Factor [Recombinant]) 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 together with the human heat shock protein 70 (HSP70) gene. (1)

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.

The specific activity of KOVALTRY is approximately 4000 IU/mg protein.

INDICATIONS AND CLINICAL USE

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.

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.

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. (see **DOSAGE AND ADMINISTRATION**)

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 **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Known hypersensitivity to mouse or hamster protein.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A (see **WARNINGS AND PRECAUTIONS, Immune**).

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 **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. (2)

Immune

The formation of neutralizing antibodies (inhibitors) to Factor VIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the Factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the 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. (3)

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.

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.

Special Populations

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.

Nursing Women

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.

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. (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

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.

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 **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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 193 previously treated patients (PTPs) patients constituted the safety population in the three phase III studies Long-term Efficacy Open-Label PrOgram in Severe Hemophilia A Disease (LEOPOLD) I, LEOPOLD II and LEOPOLD Kids Part A (see **CLINICAL TRIALS**).

The most frequently reported adverse reactions were related to potential hypersensitivity reactions, including headache (7.3%), pyrexia (4.1%), pruritus (3.1%), rash (2.6%), and abdominal discomfort (1.6%).

Clinical Trial Adverse Drug Reactions

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

The 193 PTPs (including 51 pediatric patients) were included to assess the frequency of adverse reactions in the three phase III studies (see Table 2).

Table 2 – Adverse Drug Reactions in Previously Treated Patients (PTPs) (N = 193)

	KOVALTRY N (%)
Blood and Lymphatic System Disorders	
Lymphadenopathy	2 (1.0%)
Cardiac Disorders	
Palpitation	2 (1.0%)
Sinus tachycardia	2 (1.0%)
Gastrointestinal Disorders	
Abdominal pain	4 (2.1%)
Abdominal discomfort	3 (1.6%)
Dyspepsia	4 (2.1%)
General Disorders and Administration Site Conditions	
Chest discomfort	2 (1.0%)
Injection site reactions[a]	5 (2.6%)
Pyrexia	8 (4.1%)
Immune System Disorders	
Hypersensitivity	1 (0.5%)
Nervous System Disorders	
Dizziness	2 (1.0%)
Dysgeusia	1 (0.5%)
Headache	14 (7.3%)
Psychiatric Disorders	
Insomnia	5 (2.6%)
Skin and subcutaneous tissue disorders	
Dermatitis allergic	2 (1.0%)
Pruritus	6 (3.1%)
Rash[b]	5 (2.6%)
Urticaria	1 (0.5%)
Vascular disorders	
Flushing	1 (0.5%)

a includes injection site extravasation and hematoma, infusion site pain, pruritus, and swelling
b includes rash, rash erythematous, and rash pruritic

Immunogenicity

The immunogenicity of KOVALTRY was evaluated in PTPs. During clinical trials conducted in 153 adults/adolescents PTPs (defined as having ≥150 exposure days) and 51 pediatric PTPs (defined as having ≥ 50 exposure days) diagnosed with severe hemophilia A (FVIII <1%) no case of inhibitor development occurred (see **CLINICAL TRIALS**).

DRUG INTERACTIONS

Drug-Drug Interactions

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

DOSAGE AND ADMINISTRATION

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.

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 **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 **DOSAGE AND ADMINISTRATION**, **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. (4)

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 3.

Table 3 - 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 hemarthorosis, muscle bleeding, or hematoma)	30-60%	Repeat infusion every12-24 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. This information should be taken into account when dosing or following FVIII levels in such a population (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

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. (5) There is currently no consensus among treaters to the optimal treatment schedule.

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.

Administration

KOVALTRY (Antihemophilic Factor [Recombinant]) supplied with BIO-SET Needle-less Reconstitution Set is a self-contained system that prevents needlestick injuries during reconstitution (see **WARNINGS AND PRECAUTIONS – General**).

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.

Reconstitution

Parenteral Products

KOVALTRY powder should only be reconstituted with the supplied diluent (2.5 or 5.0 mL Sterile Water for Injection) using theprefilled 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 can be achieved by following the reconstitution and/or administration steps as described below. It is important to use the administration set provided with the product for administration as it incorporates an in-line filter. In situations where the administration set provided cannot be used (eg, when infusing into a peripheral or central line), a separate filter compatible with KOVALTRY should be used.

If you have any questions about KOVALTRY and compatible separate filters contact Bayer at 1-800-265-7382 or canada.medinfo@bayer.com.

The administration set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOVALTRY through an injection filter.

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

1. Warm the unopened diluent (as needed) and the product to room temperature not to exceed 37°C.
2. Remove the cap from the concentrate. Take out the diluent prefilled syringe and remove the tip cap (Figure A). Do not remove plunger rod until step 5.

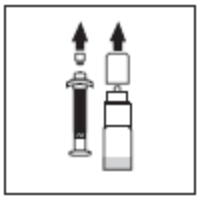


Fig. A

3. Connect the diluent prefilled syringe to the product vial by gently screwing on to the BIO-SET connection (Figure B).

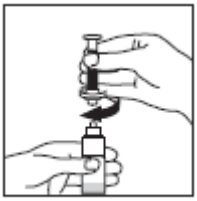


Fig. B

4. Place the vial on a rigid, non-skid surface and hold it firmly with one hand. With the other hand, strongly press down the fingerplate near the syringe tip using your thumb and index finger (Figure C) until the fingerplate meets the top edge of the BIO-SET. This confirms that the system is activated (Figure D).

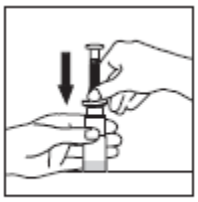


Fig. C

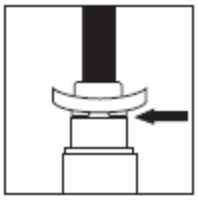


Fig. D

5. Grasp the plunger rod by the top plate and remove from carton. **Avoid touching the sides and threads of the plunger rod.** Immediately screw plunger rod into the syringe rubber stopper (Figure E).

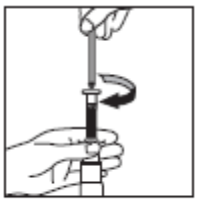


Fig. E

6. Inject the diluent into the product by pushing down the plunger rod slowly (Figure F).

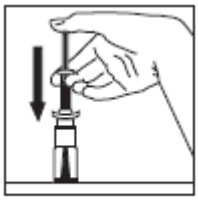


Fig. F

7. Swirl gently until completely dissolved without creating excessive foaming (Figure G).

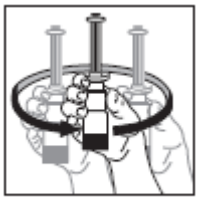


Fig. G

8. Inspect visually for particulate matter and discoloration prior to administration.
9. Invert vial/syringe and transfer the solution into syringe that was used to deliver the diluent (Figure H). Ensure that the entire contents of the reconstituted KOVALTRY vial are drawn into the syringe. Carefully remove all air by pushing the air back into the vial, but making sure you have withdrawn all of the solution.Do not use the reconstituted product if you notice any particulates or turbidity in the solution.

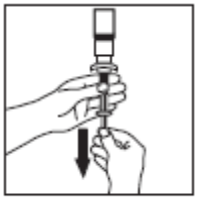


Fig. H

10. Unscrew the filled syringe to disconnect it from the empty concentrate vial (Figure I).

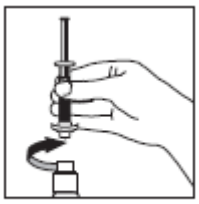


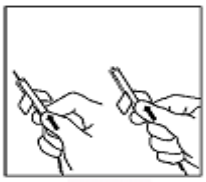
Fig. I

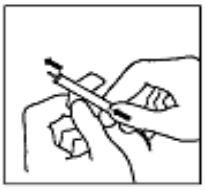
For Injection

11. Attach the filled syringe to the administration set provided and inject intravenously within 3 hours of reconstitution (Figure J).
NOTE: Firmly grasp one or both wings of the administration set to perform venipuncture; do not use the post-use needle shield for this purpose.


Fig. J

12. After infusion, lock post-use needle shield in place using one of the following methods:
    a) One-hand technique: Hold tubing in hand and advance needle shield with thumb and index finger until locked over needle tip (Figure K).
    b) Two-hand technique: Hold wing stationary and slide needle shield forward with other hand until locked over needle tip (Figure L).

K


L


13. If the same patient is to receive more than one bottle, the diluent syringe provided should be used to reconstitute the powder in the product vials as described above.
The reconstituted solutions should then be combined in a larger plastic syringe (not provided) and administered as usual (Figure J).

Table 4 - 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

OVERDOSAGE

No symptoms of overdose have been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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.

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 5 - 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)
t½ (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)
Vss (dL/kg)	0.69 (27.7)	0.66 (21.8)	0.96 (0.87-1.06)

Table 6 - 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)
t½ (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. (6)

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 **CLINICAL TRIALS**). (7)

Table 7 - 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 8 - 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 9. 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 9 - PK parameters (Geometric mean (%CV)) for KOVALTRY in PTP children <12 years based on chromogenic assay

Parameter [unit]	PTPs 0 – <6 years N = 5	PTPs 6 – <12 years N = 10	PTPs Total N = 15
	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]	0.037 (25.1)[a]	0.043 (34.8)	0.041 (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.

STORAGE AND STABILITY

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).

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KOVALTRY (Antihemophilic Factor [Recombinant]) is supplied in the following single use vials (see Table 10) and with a BIO-SET Needle-less Reconstitution Set. A prefilled diluent syringe containing Sterile Water for Injection, EP, USP for reconstitution, and a sterile administration set are also provided.

Table 10 – 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.

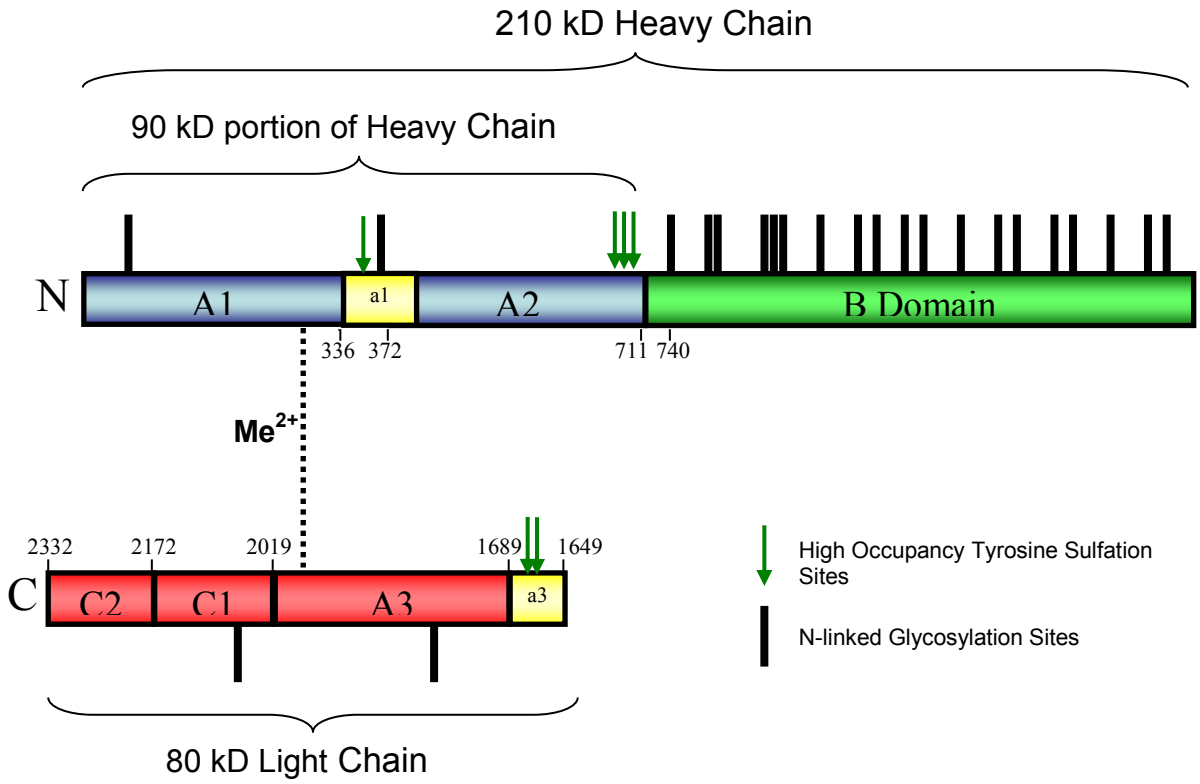
KOVALTRY is a lyophilized powder and formulated with the following inactive ingredients /excipients for the final container: 2.2% glycine, 1% sucrose, 30 mM sodium chloride, 2.5 mM calcium chloride, 20 mM histidine and 80 ppm polysorbate 80. The pH of the reconstituted product is 6.6 to 7.0. KOVALTRY 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.

PART II: SCIENTIFIC INFORMATION

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 $C_{8241}H_{12908}N_{2264}O_{2528}S_{50}$ and light chain $C_{3553}H_{5408}N_{956}O_{1026}S_{33}$



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 full length, unmodified coagulation Factor VIII. It is produced by genetically engineered Baby Hamster Kidney (BHK) cells into which the human Factor VIII gene has been introduced. (1, 8) 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. (1) Oligosaccharide characterization of the final product has shown superior glycosylation, better branching, and sialylation capping of terminal galactose residues. (9, 10) 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. (1) The cell culture process employs a continuous perfusion process and is followed by an automated continuous cell separation process.

Viral Inactivation

To ensure 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 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. (11)

CLINICAL TRIALS

Study Demographics and Trial Design

The safety, efficacy and pharmacokinetics of KOVALTRY were evaluated in three open-label, multicenter clinical trials. A total of 204 male previous treated patients (PTPs) with severe hemophilia A (≤ 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 subjects aged < 12 years old, and 50 of them had ≥ 50 EDs in the clinical trial. The median number of exposure days was 73 (range: 37 to 103).

Table 11 - Summary of Patient Demographics and Trial Design

Study #	Trial Design	Dosage of KOVALTRY	# of PTP subjects	Median (range) age (year)
LEOPOLD I (12, 13)	Open-label, multicenter	Part A: PK 50 IU/kg (compared to Kogenate FS 50 IU/kg)	26	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	30.0 (12 – 61)
		Dosing frequency 2x/week	18	40 (12-61)
		Dosing frequency 3x/week	44	29 (12-60)
		Part C: peri-operation: according to standard practice for the use of Kogenate FS.	5	37.0 (28-38)
		Extension: Prophylaxis / on-demand / peri-operation	55	31.0 (12-61)
LEOPOLD II (14)	Open-label, multicenter, randomized	Prophylaxis group by randomization: Dosing frequency 2x/week low dose (20 ─ 30 IU/kg)	28	30.0 (14 – 53)
		Dosing frequency 3x/week high dose (30 ─ 40 IU/kg)	31	27.0 (14 – 54)
		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	21	28.0 (14 – 59)
LEOPOLD KIDS (PART A) (15)	Open-label, multicenter	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	6.0 (1 – 11)
		Optional PK measurements (patients to receive exact dose of 50 IU/kg)	15	

*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.

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 12 - 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 13.

Table 13 -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)

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 14). 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 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 14 - 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 subjects were treated with KOVALTRY. 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 15 - Control and Prevention of Bleeding Episodes in Children Treated with KOVALTRY

	LEOPOLD Kids		
	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)

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). (16)

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.

DETAILED PHARMACOLOGY

Primary Pharmacology

Two sets of primary in vivo pharmacology studies directly compared the ability of KOVALTRY and another recombinant Factor VIII (rFVIII), KOGENATE FS, to protect against blood loss following tail injury in hemophilia A mice using 2 treatment scenarios, "on-demand" and prophylactic. KOVALTRY and KOGENATE FS provided equivalent protection against bleeding at dose levels of 12 or 40 IU/kg and 40 or 120 IU/kg respectively.

Safety Pharmacology

The safety pharmacology test program encompassed studies on cardiovascular and respiratory function after single intravenous administration of KOVALTRY.

Cardiovascular function (including ECG) was investigated in anesthetized beagle dogs after a single short (<5 minute) iv injection and respiratory function in conscious unrestrained rats after a single bolus iv injection. No treatment-related effects on cardiovascular function and ECG were found in dogs (highest dose tested was 400 IU/kg, or approximately 10-times the clinical dose).

Respiratory function in rats was only affected at the high dose of 400 IU/kg as expressed by transient increases in respiratory frequency (reversible within 1 hour after administration) and minute volume relative to concurrent controls. These effects were not seen in rats treated with 120 IU/kg (approximately 3-times the clinical dose).

Pharmacokinetics in animals

The PK studies used the Sprague-Dawley rat as the rodent model and the New Zealand White rabbit as the non-rodent model.

PK non-inferiority of KOVALTRY as compared to KOGENATE FS was assessed based on dose normalized area-under-the-curve (AUC) and terminal half-life parameters in both species, and non-inferiority was shown. While the ratio of AUC values for KOVALTRY / KOGENATE FS differed by a factor of 1.39 and 1.63 in rats and rabbits, respectively, and the corresponding plasma clearance of KOVALTRY compared to KOGENATE FS was 28% lower in the rat and 39% lower in the rabbit, the half-life of both compounds was not relevantly different. No relevant differences in PK parameters were observed in hemophilia A mice treated with KOVALTRY or KOGENATE FS.

TOXICOLOGY

Toxicology studies of KOVALTRY (see Table 16) 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 16 - 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 Recovery, 4/M / group	IV IV	KOVALTRY (2 lots) KOVALTRY A(2lots)	0, 400, 4000 IU/kg 0, 4000 IU/kg	KOVALTRY was well tolerated in male rats and rabbits and no treatment-related adverse 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.
	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	
Repeat-Dose Toxicity					
5-day systemic toxicity (GLP) (+ 4-week recovery, TK)	Rat, Sprague-Dawley; 10/M / group Recovery; 5/M / group	IV IV	KOVALTRY KOVALTRY	0, 40, 120, 400 IU/kg 0, 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.
	Rabbit, New Zealand White; 6/M / group Recovery; 3/M / group	IV IV	KOVALTRY KOVALTRY	0, 40, 120, 400 IU/kg 0, 400 IU/kg	
Genotoxicity					
In vitro Mutagenicity (Mouse lymphoma assay, GLP)	L5178Y cell line	*In vitro*	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.

Table 16 - Toxicology Program

Type of Study/ Duration	Subjects (Species, Strain; No. /Sex / Group)	Route of Administration	Compound administered	Doses	Key Findings
Other toxicity studies					
Immunogenity (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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICATION

PATIENT MEDICATION INFORMATION

Pr 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 to reduce the occurrence of spontaneous bleeding episodes in hemophilia A.
- 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:

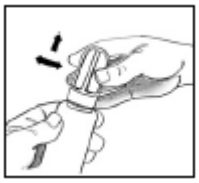
- No interactions with other medicines are known. However, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

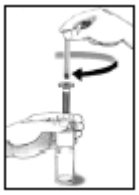
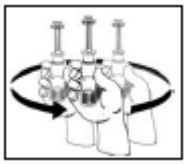
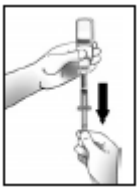
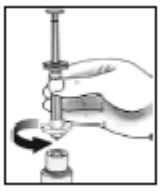
How to take KOVALTRY:

- 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 (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:

1. Prepare **A. Open** The easiest way to remove the cap from the vials is to move the top from side-to-side while pulling upward at the same time. This breaks the small plastic tabs that connect the cap to the top of the vial.	
B. Remove Tip Cap Remove the tamper-evident tip cap from the syringe. Separate the tip cap from the syringe by gently breaking it off. Hold the syringe in one hand while snapping off the tip cap with the other hand. Do not try to twist it off. Move it from side-to-side.	

C. Connect Syringe Connect the prefilled syringe to the powder vial by gently screwing it on clockwise on to the top of the vial until finger tight. Do not overtighten.	
2. Activate **A. Activate (Spike the vial)** Place the vial on a solid, non-skid surface. Hold the vial **firmly** with one hand. With the other hand, place your thumb and forefinger on the fingerplate of the syringe and press down firmly on the fingerplate until it meets the top of the powder vial. **This is the most critical step in the process.** If the syringe is not pushed down firmly enough, the system will not be fully activated.	
B. Connect Plunger Rod Grasp the plunger rod at the top. Avoid contact with the rest of the plunger rod. Immediately connect it to the syringe by screwing the plunger rod clockwise into the rubber stopper.	
C. Inject Inject diluent into the vial by **slowly** pressing down the plunger rod. **Pushing down the syringe too quickly may cause foaming in the vial. If this occurs, wait until the foam subsides before continuing.**	
D. Mix Mix the diluent and powder by swirling **gently** and **slowly**. DO NOT SHAKE THE VIAL. Be sure the powder is completely dissolved before using.	
3. Transfer **A. Transfer** Invert the vial, with the syringe still attached and smoothly draw all the solution into the syringe. Tilt the vial to the side and back to check that all remaining solution has been drawn into the large opening in the rubber stopper. **Carefully remove all air by pushing the air back into the vial, but making sure you have withdrawn all of the solution.**	 
B. Disconnect Disconnect the syringe from the empty vial by unscrewing it counterclockwise. DO NOT PULL THE SYRINGE FROM THE VIAL WITHOUT UNSCREWING IT FIRST.	

C. Infuse Attach the syringe to the butterfly set by screwing it in clockwise and follow the infusion instructions provided with Kovaltry with BIO-SET.	

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. If this dose does not control your bleeding your doctor may consider giving you an additional product, Factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with hemophilia A. Speak to your doctor if you would like further information on this.
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 have taken too much KOVALTRY, contact your 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: **WARNINGS AND PRECAUTIONS**.

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

- lymph nodes enlarged
- heart palpitations
- rapid heartbeat

- stomach pain
- stomach discomfort
- indigestion
- fever
- chest discomfort
- local reactions where you injected the medication
- headache
- dizziness
- trouble falling asleep
- rash/itchy rash, allergic dermatitis, itching

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

- 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)
- urticaria (swelling)

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, talk to your healthcare professional.

Reporting Side Effects

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

3 ways to report:

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

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

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

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.

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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 [http://hc-sc.gc.ca/index-eng.php]; the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This leaflet was prepared by

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