HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KOVALTRY safely and effectively. See full prescribing information for KOVALTRY.

KOVALTRY [Antihemophilic Factor (Recombinant)]
Lyophilized Powder for Solution for Intravenous Injection – Reconstitution with BIO-SET
Initial U.S. Approval: 2016

---------- **INDICATIONS AND USAGE** ----------
KOVALTRY®, Antihemophilic Factor (Recombinant), is a recombinant, human DNA sequence derived, full length Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

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

KOVALTRY is not indicated for the treatment of von Willebrand disease (1).

---------- **DOSAGE AND ADMINISTRATION** ----------
For intravenous use after reconstitution only.

Control of bleeding episodes and perioperative management (2.1)

- Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected/observed recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg).
- Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg).

Routine prophylaxis (2.1)

- Adults and adolescents: 20 - 40 IU/kg 2 or 3 times per week.
- Children ≤12 years old: 25 - 50 IU/kg 2 times per week, 3 times per week or every other day.

---------- **DOSAGE FORMS AND STRENGTHS** ----------
KOVALTRY is available as lyophilized powder in single-use vials containing nominally 250, 500, 1000, 2000, or 3000 IU. Each vial of KOVALTRY contains the labeled amount of recombinant Factor VIII in IU (3).

---------- **CONTRAINDICATIONS** ----------
Do not use in patients who have history of hypersensitivity reactions to the active substance, mouse or hamster protein, or other constituents of the product (4).

---------- **WARNINGS AND PRECAUTIONS** ----------

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue treatment with KOVALTRY and administer appropriate treatment (5.1).
- Development of Factor VIII neutralizing antibodies can occur. Perform an assay that measures Factor VIII inhibitor concentration if expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled as expected with administered dose (5.2, 5.5).

---------- **ADVERSE REACTIONS** ----------
The most frequently reported adverse reactions in clinical trials (≥3%) were headache, pyrexia, and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **USE IN SPECIFIC POPULATIONS** ----------
Pediatric Use: Due to higher clearance (body weight adjusted) in children ≤12 years of age, higher or more frequent dosing may be needed (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 3/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KOVALTRY, Antihemophilic Factor (Recombinant), is a recombinant, human DNA sequence derived, full length Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

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

KOVALTRY is not indicated for the treatment of von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Dosage and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- Each vial label of KOVALTRY states the Factor VIII potency in international units (IU). One IU is defined by the current WHO (World Health Organization) international standard (IS) for Factor VIII concentrate.
- Potency assignment for KOVALTRY is determined using a chromogenic substrate assay. A field study involving 41 clinical laboratories from around the world measured recoveries of KOVALTRY spiked into hemophilic plasma. The results of the field study indicated that the Factor VIII activity of KOVALTRY can be accurately measured in plasma using either a one-stage clotting or chromogenic substrate assay according to routine methods of the testing laboratory.
- The required dose for a desired Factor VIII level expressed as IU/dL (or % of normal) can be estimated using the following formula:

  Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected/observed recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg)

  The expected *in vivo* peak increase of Factor VIII level expressed as IU/dL (or % of normal) can be estimated using the following formula:

  Estimated increment of Factor VIII (IU/dL or % of normal) = [Total dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

  Examples (assuming patient's baseline Factor VIII is <1%):

  1. A peak of 50% is required in a 20 kg child. In this situation, the required dose of KOVALTRY would be 20 kg x 50 IU/dL x 0.5% (for recovery of 2 IU/dL per IU/kg) = 500 IU
  2. A dose of 2000 IU of KOVALTRY administered to a 50 kg patient should be expected to result in post-infusion Factor VIII increase of 2000 IU / 50 kg (body weight) x 2 IU/dL per IU/kg = 80 IU/dL (80% of normal)

- Adjust dose to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, incremental recovery) and clinical responses to KOVALTRY.

<u>On-demand Treatment and Control of Bleeding Episodes</u>

A guide for dosing KOVALTRY for the on-demand treatment and control of bleeding episodes is provided in Table 1. The goal of treatment is to maintain a plasma Factor VIII activity level at or above the plasma levels (in % of normal or in IU/dL) outlined in Table 1.

Table 1: Dosing for Control of Bleeding Episodes

Degree of Bleeding	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (Early hemarthrosis, minor muscle, oral bleeds)	20–40	Repeat every 12–24 hours	At least 1 day, until bleeding episode as indicated by pain is resolved or healing is achieved
Moderate (More extensive hemarthrosis, muscle bleeding, or hematoma)	30–60	Repeat every 12–24 hours	3 to 4 days or more until pain and acute disability are resolved
Major (intracranial, intra-abdominal or intrathoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath, life or limb threatening hemorrhage)	60–100	Repeat every 8–24 hours	Until bleeding is resolved

Perioperative Management of Bleeding

A guide for dosing KOVALTRY during surgery (perioperative management) is provided in Table 2. The goal of treatment is to maintain a plasma Factor VIII activity level at or above the plasma level (in % of normal or in IU/dL) outlined in Table 2. During major surgery, monitoring with appropriate laboratory tests, including serial Factor VIII activity assays, is highly recommended *[see Warnings and Precautions (5.5)]*.

Table 2: Dosing for Perioperative Management

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor (Such as tooth extraction)	30–60 (pre- and post-operative)	Repeat every 24 hours	At least 1 day until healing is achieved
Major (Such as intracranial, intra-abdominal, intrathoracic, or joint replacement surgery)	80–100 (pre- and post-operative)	Repeat every 8–24 hours	Until adequate wound healing is complete, then continue therapy for at least another 7 days to maintain Factor VIII activity of 30–60% (IU/dL)

Routine Prophylaxis

- Individualize the patient's dose based on clinical response.
- Adults and adolescents: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week.
- Children ≤12 years old: 25 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirements *[see Use in Specific Populations (8.4)]*.

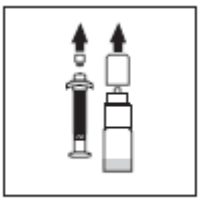
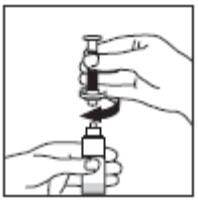
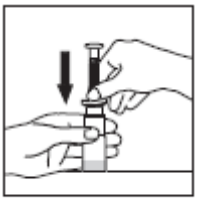
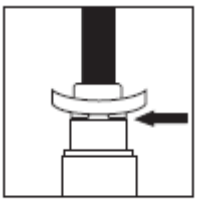
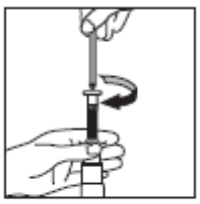
2.2 Preparation and Reconstitution

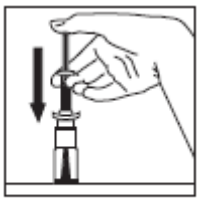
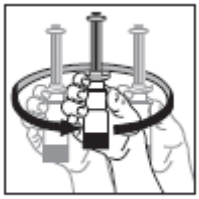
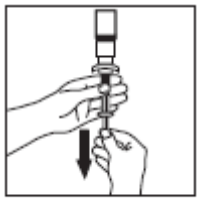
- Reconstitute and administer KOVALTRY with the components provided with each package. If any component of the package is opened or damaged, do not use this component.

- For any questions about the handling, reconstitution and administration of KOVALTRY, contact Bayer Medical Communications at 1-888-84-BAYER (1-888-842-2937).

The procedures below are provided as general guidelines for the reconstitution of KOVALTRY with BIO-SET®, a needleless self-contained reconstitution system.

Reconstitution

1. Prepare the product under aseptic conditions.	
2. Warm the unopened diluent (as needed) and the concentrate to a temperature not to exceed 37°C or 99°F.	
3. Remove the cap from the concentrate. Take out the prefilled diluent syringe and remove the tip cap. (Fig. A).	 Fig. A
4. Connect the prefilled diluent syringe to the concentrate vial by gently screwing on to the BIO-SET connection (Fig. B).	 Fig. B
5. 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 (Fig. C) until the fingerplate meets the top edge of the BIO-SET. This confirms that the system is activated (Fig. D).	 Fig. C  Fig. D
6. 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 (Fig. E).	 Fig. E

7. Inject the diluent into the concentrate by pushing down the plunger rod slowly (Fig. F).	 Fig. F
8. Swirl gently until completely dissolved without creating excessive foaming (Fig. G).	 Fig. G
9. Invert vial/syringe and transfer the solution into syringe that was used to deliver the diluent (Fig. 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.	 Fig. H
10. Unscrew the filled syringe to disconnect it from the empty concentrate vial (Fig. I).	 Fig. I
11. Attach the filled syringe to the administration set provided and immediately inject intravenously (Fig. J).	 Fig. J
12. If the same patient is to receive more than one vial, 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 administer as usual (Fig. J).	

Pooling

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.

2.3 Administration

For intravenous use only.

- Inspect reconstituted KOVALTRY visually for particulate matter and discoloration prior to administration. Do not use if you notice any particulate matter or discoloration and immediately contact Bayer Medical Communications at 1-888-84-BAYER (1-888-842-2937).
- Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.

- Use the administration set provided with the product as it incorporates an in-line filter. In situations where the administration set provided cannot be used (e.g., when infusing into a peripheral or central line), use a separate filter compatible with KOVALTRY.

  NOTE: Do not use the administration set provided with the product to draw 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. For any questions about compatible separate filters, contact Bayer Medical Communications at 1-888-84-BAYER (1-888-842-2937).

- Infuse KOVALTRY intravenously over a period of 1 to 15 minutes. Adapt the rate of administration to the response of each individual patient.

3 DOSAGE FORMS AND STRENGTHS

KOVALTRY is available as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000, 2000, or 3000 IU of recombinant Factor VIII per vial.

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

4 CONTRAINDICATIONS

KOVALTRY is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, to any of the excipients, or to mouse or hamster proteins *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible with KOVALTRY. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension and nausea. Discontinue KOVALTRY if symptoms occur and seek immediate emergency treatment.

KOVALTRY may contain trace amounts of mouse and hamster proteins *[see Description (11)]*. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.2 Neutralizing Antibodies

Neutralizing antibody (inhibitor) formation can occur following administration of KOVALTRY. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all Factor VIII products *[see Adverse Reactions (6.1)]*. Carefully monitor patients for the development of Factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled as expected with administered dose, suspect the presence of an inhibitor (neutralizing antibody) *[see Warnings and Precautions (5.5)]*.

5.3 Cardiovascular Risk Factors

Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with Factor VIII.

5.4 Catheter-related Infections

Catheter-related infections may be observed when KOVALTRY is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.

5.5 Monitoring Laboratory Tests

- Monitor plasma Factor VIII activity levels using a validated test to confirm that adequate Factor VIII levels have been achieved and maintained *[see Dosage and Administration (2.1)]*.

- Monitor for development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained or if bleeding is not controlled with the expected dose of KOVALTRY. Use Bethesda Units (BU) to report inhibitor titers.

6 ADVERSE REACTIONS

The most frequently reported adverse reactions in clinical trials (≥3%) were headache, pyrexia, and pruritus (see Table 3).

6.1 Clinical Trials Experience

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

The safety profile of KOVALTRY was evaluated in 193 previously treated patients (PTPs) (inclusive of 51 pediatric patients <12 years of age) with at least three months of exposure to KOVALTRY. The safety analysis was done using a pooled database from three multi-center, prospective, open-label clinical studies. The median time on study for patients ≥12 years of age was 372 days with a median of 159 exposure days (EDs). The median time on study for patients <12 years of age was 182 days with a median of 73 EDs. Subjects who received KOVALTRY for perioperative management (n=5) with treatment period of 2 to 3 weeks and those who received single doses of KOVALTRY for PK studies (n=6) were excluded from safety analysis. Table 3 lists the adverse reactions reported during clinical studies. The frequency, type, and severity of adverse reactions in children are similar to those in adults.

Table 3: Adverse Reactions in PTPs (N=193)

MedDRA Primary System Organ Class Preferred term	**Frequency** **N (%)**
Blood and the 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	
Pyrexia	8 (4.1%)
Chest discomfort	2 (1.0%)
Injection site reactions[a]	5 (2.6%)
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

All clinical trial subjects were monitored for neutralizing antibodies (inhibitors) to Factor VIII by the modified Bethesda assay using blood samples obtained prior to the first infusion of KOVALTRY, at defined intervals during the studies and at the completion visit.

Clinical trials (Phases 1 through 3) with KOVALTRY evaluated a total of 204 pediatric and adult patients diagnosed with severe hemophilia A (Factor VIII <1%) with previous exposure to Factor VIII concentrates ≥50 EDs, and no history of inhibitors.

In the completed studies, no PTP developed neutralizing antibodies to Factor VIII. In an ongoing extension study, a 13 year old PTP had a titer of 0.6 BU after 550 EDs concurrent with an acute infection and positive IgG anticardiolipin antibodies. The Factor VIII recovery was 2.2 IU/dL per IU/kg, annualized bleeding rate (ABR) was zero, and no change in therapy was required.

In an actively enrolling clinical trial in PUPs, 6 of 14 treated subjects (42.9% with a 95% Confidence Interval of 17.7-71.1%) developed an inhibitor. Of these, 3 subjects (21.4%) had high titer inhibitors, and 3 subjects (21.4%) had transient low titer inhibitors for which no change in therapy was required.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to KOVALTRY with the incidence of antibodies to other products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with KOVALTRY use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using KOVALTRY. It is not known whether KOVALTRY can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOVALTRY should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Safety and efficacy studies with KOVALTRY have been performed in pediatric PTPs. Body weight adjusted clearance of Factor VIII in children ≤12 years of age is higher than in adults and adolescents. Consider higher or more frequent dosing in children to account for this difference in clearance *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical studies with KOVALTRY did not include patients aged 65 and over to determine whether or not they respond differently from younger patients. However, clinical experience with other Factor VIII products has not identified differences between the elderly and younger patients. As with any patient receiving recombinant Factor VIII, dose selection for an elderly patient should be individualized.

11 DESCRIPTION

KOVALTRY, Antihemophilic Factor (Recombinant), is a sterile, non-pyrogenic, white to slightly yellow powder for reconstitution contained in a single-use vial. The final product does not contain any preservative. The reconstituted product is indicated for intravenous administration. The product is available in 250 IU, 500 IU, 1000 IU, 2000 IU, or 3000 IU nominal potencies; however, for each dosage strength the actual, assayed Factor VIII potency is directly printed on each vial label. The container closure system consists of a 10 mL, Type I glass vial sealed with a bromobutyl grey stopper and a reconstitution cap. The reconstitution cap was designed to connect with the sterile water for injection (sWFI), prefilled diluent syringe. KOVALTRY is formulated with the following excipients: 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. Intravenous administration of sucrose contained in KOVALTRY will not affect blood glucose level.

The active substance in KOVALTRY is the unmodified full length recombinant Factor VIII glycoprotein comprising the human derived amino acid sequence. Post-translational modifications are similar to those of endogenous Factor VIII including glycosylation sites and sulfation of tyrosine sites. Manufacturing and quality controls ensure that both galactose-alpha-1,3-galactose (alpha-Gal) and N-glycolyl neuraminic acid (NGNA) content are below the 1% limit of detection established for each analytical method.

KOVALTRY is produced by a genetically engineered Baby Hamster Kidney (BHK) cell line into which the human Factor VIII gene was introduced together with the human heat shock protein 70 (HSP 70) gene. HSP 70 is an intracellular protein that improves proper folding of the Factor VIII protein. While KOVALTRY and Kogenate FS have the same protein backbone, human- and animal-derived raw materials are not added to the cell culture, purification, or formulation processes for KOVALTRY. In the manufacturing process for KOVALTRY, recombinant Factor VIII is secreted into cell culture medium and is purified from process- and product-related impurities using a series of chromatography and filtration steps. The production process incorporates two dedicated viral clearance steps: (1) a detergent treatment step for inactivation and (2) a 20 nanometer filtration step for removal of viruses and potential protein aggregates.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KOVALTRY temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

Plasma clotting time as measured by the activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Treatment with KOVALTRY normalizes the aPTT.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of KOVALTRY were investigated in PTPs (0 to 61 years of age) with severe Hemophilia A following administration of 50 IU/kg of KOVALTRY. The PK parameters of KOVALTRY are presented in Table 4 (one-stage clotting assay) and Table 5 (chromogenic substrate assay). The PK of KOVALTRY were similar between single and repeat dosing (in 19 subjects following 6 to 12 months of prophylaxis).

Table 4: Pharmacokinetic Parameters [Arithmetic Mean ± SD] for KOVALTRY (50 IU/kg dose), One-Stage Clotting Assay

Parameter [unit]	12 to 17 yrs (N=5)	≥18 yrs (N=21)
AUC [IU*h/dL]	1013.9 ± 286.8	1601.3 ± 520.0
C_{max} [IU/dL]	91.7 ± 28.7	99.7 ± 14.9
$t_{½}$ [h]	11.7 ± 1.11	14.3 ± 3.7
MRT_{IV} [h]	16.1 ± 0.8	19.8 ± 5.7
V_{ss} [dL/kg]	0.85 ± 0.24	0.63 ± 0.11
CL [dL/h/kg]	0.053 ± 0.017	0.035 ± 0.012

AUC: area under the curve
C_{max}: maximum drug concentration in plasma after single dose
$t_{½}$: terminal half-life
MRT_{IV}: mean residence time after an IV administration
V_{ss}: apparent volume distribution at steady-state
CL: clearance

The PK parameters of KOVALTRY for 8 subjects in age group 0 to <6 years and 10 subjects in age group 6 to <12 years are shown in Table 5. In general, children <12 years of age demonstrated lower plasma concentrations when compared to PTP children ≥12 years of age.

Table 5: Pharmacokinetic Parameters [Arithmetic Mean ± SD] for KOVALTRY (50 IU/kg dose), Chromogenic Substrate Assay

Parameter [unit]	0 to <6 yrs (N=8)	6 to <12 yrs (N=10)[b]	12 to 17 yrs (N=5)	≥18 yrs (N=21)
AUC [IU*h/dL]	1544.7 ± 387.1[a]	1214.5 ± 395.1	1572.0 ± 448.0	2103.4 ± 702.8
C_{max} [IU/dL]	89.6 ± 27.4	81.6± 17.8	132.5 ± 46.3	133.1 ± 20.4
$t_{½}$ [h]	12.1 ± 2.7[a]	12.0 ± 2.1	14.4 ± 5.5	14.2 ± 3.5
MRT_{IV} [h]	17.7 ± 3.6[a]	17.8 ± 2.9	19.8 ± 5.8	19.9 ± 4.9
V_{ss} [dL/kg]	0.57 ± 0.13[a]	0.79 ± 0.23	0.71 ± 0.39	0.50 ± 0.11
CL [dL/h/kg]	0.033 ± 0.009[a]	0.045 ± 0.016	0.034 ± 0.010	0.027 ± 0.010

[a] n=7

[b] One subject considered PK outlier was excluded

Incremental Recovery analysis after 6 months of prophylactic treatment yielded comparable results with incremental recovery after the first dose (see Table 6).

Table 6: Incremental Recovery in PTPs

	0 to <6 yrs N=25	6 to 12 yrs N=25	≥12 yrs N=115
Chromogenic substrate assay results[a] Median (Q1; Q3) (IU/dL per IU/kg)	1.6 (1.3; 1.9)	1.7 (1.4; 2.0)	2.3 (1.8; 2.6)
One-stage assay results[a] Median (Q1; Q3) (IU/dL per IU/kg)	-	-	2.2 (1.8; 2.4)

[a]Start of study

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of KOVALTRY or other studies to determine the effects of KOVALTRY on fertility have not been performed. KOVALTRY was negative in the modified *in-vitro* (Mammalian Mutation and Chromosome Aberration Assay with Mouse Lymphoma Cells) genotoxicity test. KOVALTRY is expected to have no mutagenic potential.

14 CLINICAL STUDIES

The safety and efficacy of KOVALTRY for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis in subjects with severe hemophilia A (<1% Factor VIII) was evaluated in three international (including U.S.) clinical studies. Immunocompetent subjects with severe hemophilia A (Factor VIII activity ≤1%) and no history of Factor VIII inhibitors were eligible for the trials.

Study 1: a multi-center, open-label, cross-over, uncontrolled, study in adolescent and adult (age ≥12 years to <65 years) PTPs (≥150 EDs) evaluated the pharmacokinetics, efficacy and safety of routine prophylaxis, and perioperative management of bleeding of KOVALTRY (see Table 7). The primary efficacy variable was ABR. The prophylactic regimen was 20 to 50 IU/kg two or three times per week in which the dosing frequency was assigned by the investigator based on the subject's individual requirements.

Study 2: a multi-center, open-label, cross-over, uncontrolled, randomized study in adolescent and adult (age ≥12 years to <65 years) PTPs (≥150 EDs) evaluated the superiority of prophylaxis over on-demand treatment with KOVALTRY over a one-year treatment period (see Table 7). The primary efficacy variable was ABR. The prophylactic regimen was 20 to 30 IU/kg two times per week or 30 to 40 IU/kg three times per week and the treatment group was assigned by randomization.

Study 3: a multi-center, open-label, uncontrolled study in pediatric (age ≤12 years) PTPs (≥50 EDs) evaluated the pharmacokinetics, efficacy and safety of routine prophylaxis, and perioperative management of bleeding of KOVALTRY (see Table 8). The primary efficacy variable was annualized number of total bleeds during routine prophylaxis that occurred within 48 hours following previous prophylaxis infusion. ABR during prophylaxis, independent of time of infusion, was also analyzed. The prophylactic regimen was 25 to 50 IU/kg at frequencies of either 2 times per week, 3 times per week or every other day and could be adapted to individual subject's need by the investigator.

In all studies, treatments of breakthrough bleeds and perioperative management were at the investigator's discretion based on standard of care.

A total of 204 subjects were enrolled in the completed clinical trials, 153 subjects ≥12 years of age and 51 subjects <12 years of age. One hundred-forty (140) subjects were treated for at least 12 months, and 43 of these subjects were treated for 24 months.

Table 7: Overview of Study 1 (Prophylaxis Treatment Phase) and Study 2

	Study 1 (N=62)	**Study 2 (N=80)**
Age: mean ± SD	31.5 ± 12.7 years	29.6 ± 11.0 years
Previous treatment: %	Prophylaxis: 80.6%	On-demand: 100%
Number of Target joints at baseline: mean ± SD	1.4 ± 1.3	3.0 ± 2.1
Joint hemorrhage history (during 12 months prior to study): mean ± SD of joint bleeds	8.0 ± 11.9	32.1 ± 23.8

Table 8: Overview of Study 3

	Study 3	
	PTPs 0 to <6 yrs (N=25)	**PTPs 6 to 12 yrs (N=26)**
Age: mean ± SD (range)	3.8 ± 1.3 years (1 - 5)	8.8 ± 1.8 years (6 - 11)
Previous treatment: %	Prophylaxis: 92.0%	Prophylaxis: 65.4%
Number of Target joints at baseline: mean ± SD	0.2 ± 0.4	0.7 ± 1.1

14.1 On-demand Treatment and Control of Bleeding Episodes

Adolescents and Adults

A total of 1892 bleeding episodes in 110 subjects were treated with KOVALTRY in Study 1 and Study 2 (see Table 9). The majority of the bleeding episodes were spontaneous, localized in joints, and mild to moderate in severity.

In Study 1 and Study 2, the treatment responses in a total of 1859 treated bleeds were assessed by the subjects compared to their previous treatment experience.

Table 9: On-demand Treatment and Control of Bleeding Episodes in Adolescents and Adults Treated with KOVALTRY

Characteristics of Bleeding Episodes	Study 1		Study 2	
	Prophylaxis Main Study N=62	Prophylaxis Extension N=55	Prophylaxis N=59	On-demand N=21
Total number of bleeds	241	154	293	1204
Spontaneous: n/total (%)	153/241 (63.5%)	79/150[a] (52.7%)	209/283[a] (73.9%)	943/1202[a] (78.5%)
Trauma: n/total (%)	79/241 (32.8%)	70/150[a] (46.7%)	74/283[a] (26.1%)	258/1202[a] (21.5%)
Joint bleeds: n/total (%)	191/241 (79.3%)	120/154 (77.9%)	255/293 (87.0%)	924/1197[a] (77.2%)
Mild/moderate: n/total (%)	215/241 (89.2%)	130/153[a] (84.9%)	260/293 (88.8%)	1092/1196[a] (91.3%)
% of bleeds treated with ≤2 infusions	87.0%		96.2%	95.3%
Response to treatment of bleeds assessed as "Excellent" or "Good": n/total[b] (%)	190/235 (80.9%)	107/149 (71.8%)	172/279 (61.6%)	834/1196 (69.7%)
Median dose per infusion (range)	31.6 IU/kg (14 - 67 IU/kg)		29.4 IU/kg (19 - 49 IU/kg)	22.0 IU/kg (11 - 35 IU/kg)

[a]Total number excluding uncharacterized bleeds
[b]The % is calculated from number of treated bleeds assessed for response

Children 12 Years of Age and Younger

A total of 97 bleeding episodes in 28 pediatric subjects were treated with KOVALTRY. Majority (96.9%) 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 dose of KOVALTRY for the treatment of breakthrough bleeds was 36.94 IU/kg per infusion (range 20.8–71.6 IU/kg).

Assessment of response to treatment of bleeds was as follows:

Excellent: Abrupt pain relief and/or improvement in signs of bleeding with no additional infusion administered; Good: Definite pain relief and/or improvement in signs of bleeding but possibly requiring more than one infusion for complete resolution; Moderate: Probable or slight improvement in signs of bleeding with at least one additional infusion for complete resolution; Poor: No improvement at all between infusions or condition worsens.

The hemostatic efficacy in on-demand treatment of bleeds was assessed as either "good" or "excellent" in 90.1% of cases (97.8% in the younger age group and 81.0% in the older age group). Majority of bleeds (89.7%) were successfully treated with ≤2 infusions. Response to treatment was similar for children aged 0 to <6 compared to 6 to 12 years of age (see Table 10).

Table 10: On-demand Treatment and Control of Bleeding Episodes in Children Treated with KOVALTRY

Characteristics of Bleeding Episodes	Study 3		
	PTPs 0 to <6 yrs (N=25)	PTPs 6 to 12 yrs (N=26)	PTPs 0 to 12 yrs (N=51)
Total number of bleeds	52	45	97
Spontaneous: n/total (%)	8/44[a] (18.2%)	12/37[a] (32.4%)	20/81[a] (24.7%)
Trauma: n/total (%)	36/44[a] (81.8%)	23/37[a] (62.2%)	59/81[a] (72.8%)
Joint bleeds: n/total (%)	10/52 (19.2%)	22/45 (48.9%)	32/97 (33.0%)
Mild/moderate: n/total (%)	50/52 (96.2%)	44/45 (97.8%)	94/97 (96.9%)
% of bleeds treated with ≤2 infusions	92.4%	86.7%	89.7%
Response to treatment of bleeds assessed as "Excellent" or "Good": n/total[b] (%)	43/44 (97.8%)	30/37 (81.0%)	73/81 (90.1%)
Median dose per 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 number of treated bleeds
[b]The % is calculated from number of treated bleeds assessed for response

14.2 Perioperative Management

A total of 14 major and 46 minor surgeries were performed in 44 previously treated subjects (43 adults and adolescents and 1 child under 12 years of age) with severe hemophilia A. Seven of the 14 major surgeries were orthopedic procedures, including joint replacement. Approximately 51% of the minor surgeries were dental extractions. All subjects received KOVALTRY as bolus infusions. In the adolescent and adult subjects, the initial KOVALTRY doses administered ranged between 3000–5000 IU. The median total dose on the day of surgery was 107.5 IU/kg (range 60–207 IU/kg). 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).

The blood loss, during and after surgery, was within expected ranges. Hemostatic control was assessed by surgeons as "good" (perioperative bleeding slightly but not clinically significantly increased over expectations for the non-hemophilic patient; treatment similar to non-hemophilic patient) or "excellent" (perioperative blood loss similar to the non-hemophilic patient).

14.3 Routine Prophylaxis

Adolescents and Adults

A total of 140 subjects were treated with KOVALTRY for at least 12 months with median (range) 157 EDs (25-178) in Study 1, [305 EDs (25-355) inclusive of extension phase], and 153 EDs (103-187) in Study 2 (see Table 11). In both studies, subjects in the Intent-to-Treat (ITT) population received 95% to 100% of the prescribed number of prophylaxis infusions.

Table 11: Prophylaxis Treatment with KOVALTRY in Adolescents and Adults – Treatment Exposure

	Study 1 (N=62)[a]	Study 2 (N=59)
Median nominal prophylaxis dose/ infusion (range)		
All	31.2 IU/kg (21 - 43 IU/kg)	31.7 IU/kg (21 - 42 IU/kg)
Prophylaxis 2 times per week	35.0 IU/kg (21 - 42 IU/kg)	30.4 IU/kg (21 - 34 IU/kg)
Prophylaxis 3 times per week	31.1 IU/kg (24 - 43 IU/kg)	37.4 IU/kg (30 - 42 IU/kg)
Treatment duration	1 year main study	1 year

Study 1: 2 times per week (n=18); 3 times per week (n=44)
Study 2: 2 times per week (n=28); 3 times per week (n=31)
[a]Study 1 included PK, safety and efficacy of prophylaxis and hemostasis during surgeries. Prophylaxis phase data are presented.

The mean and median ABR for the ITT population in Study 1 was 3.8 ± 5.2 and 1 bleed/year, respectively. In Study 2, comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis in an ANOVA demonstrated a statistically significant difference ($p<0.0001$) in the median ABR in subjects receiving on-demand therapy (60 bleeds per year) as compared to subjects receiving prophylaxis (2 bleeds per year). In Study 2, mean ABR in subjects receiving on-demand therapy was 57.7 ± 24.6 versus 4.9 ± 6.8 in the subjects receiving prophylaxis.

Table 12: ABR in Adolescent and Adult Subjects

	Study 1 (N=62)		Study 2 (N=59)	
	2 times per week (n=18)	3 times per week (n=44)	2 times per week (n=28)	3 times per week (n=31)
ABR Median (IQR[a] Q1; Q3)				
All Bleeds	1.0 (0.0; 8.0)	2.0 (0.5; 5.0)	4.0 (0.0; 8.0) Month 1-6[b]: 4.1; Month 7-12[b]: 1.1	2.0 (0.0; 4.9) Month 1-6[b]: 2.0; Month 7-12[b]: 2.0
Spontaneous Bleeds	0.5 (0.0; 2.0)	1.0 (0.0; 3.9)	2.0 (0.0; 6.5)	0.0 (0.0; 3.0)
Joint Bleeds	0.5 (0.0; 7.0)	1.8 (0.0; 3.0)	2.5 (0.0; 7.5)	1.0 (0.0; 4.0)
Subjects with Zero Bleeding Episodes[c] % (n)	37.5% (6/16[d])	62.5% (10/16[d])	28.6% (8/28[e])	25.8% (8/31[e])

[a]IQR = Interquartile Range
[b]Month 1 - 6 refers to the first six months of the treatment period and Month 7 - 12 refer to the second six months of the treatment period
[c]Observation of one-year treatment period
[d]n=total number of subjects with zero bleeds
[e]n=total number of subjects randomized to treatment arms

The ABR for subjects (n=21) receiving on-demand therapy in Study 2 [median (IQR Q1; Q3)] for all bleeds: 60 (41.7; 76.3); spontaneous bleeds: 42.1 (24.3; 61.3); joint bleeds: 38.8 (24.3; 60.0).

Children 12 Years of Age and Younger

A total of 51 PTPs were treated with KOVALTRY for at least 6 months with median (range) 73 EDs (37 - 103) (see Table 13). Subjects received >95% of the prescribed number of prophylaxis infusions.

Table 13: Prophylaxis Treatment with KOVALTRY in Children 12 Years of Age or Younger – Treatment Exposure

	Study 3	
	PTPs 0 to <6 yrs (N=25)	**PTPs 6 to 12 yrs (N=26)**
Treatment regimen[a] during study (6 months) n (%)		
2 times per week	9 (36%)	13 (50%)
3 times per week or every other day	16 (64%)	13 (50%)
Nominal prophylaxis dose per infusion, median (range)	36.4 IU/kg (21 - 58 IU/kg)	31.8 IU/kg (22 - 50 IU/kg)

[a]Treatment regimen at the start of the study. Study duration was six months.

In children 12 years of age and younger (n=51), the median (IQR Q1; Q3) ABR within 48 hours after prophylactic infusion was 0 (0; 4) for all bleeds, and 0 (0; 0) for spontaneous and joint bleeds. The median (IQR Q1; Q3) ABR during prophylactic treatment independent of time of infusion was 1.9 (0; 6) for all bleeds, 0 (0; 0) for spontaneous bleeds and 0 (0; 2) for joint bleeds. The mean ABR within 48 hours after prophylactic infusion was 2.04 ± 2.91. The mean ABR at any time during the prophylaxis regimen was 3.75 ± 4.98.

In both age groups (0 to <6 years and 6 to 12 years), the ABR for spontaneous bleeds and joint bleeds within 48 hours after prophylactic treatment [ABR median (IQR Q1; Q3)] was 0 (0; 0). The median (IQR Q1; Q3) annualized number of spontaneous bleeds during prophylactic treatment independent of time of infusion was 0 (0; 0). The median (IQR Q1; Q3) annualized number of joint bleeds during prophylactic treatment independent of time of infusion was 0 (0; 1.9) in 0 to <6 years age group and 0 (0; 2.1) in 6 to 12 years age group (see Table 14).

The majority (32/53) of bleeds that occurred within 48 hours after a previous prophylaxis infusion were trauma related. Twenty-three (45.1%) subjects reported no bleeds during the six-month prophylaxis period.

Table 14: ABR in Children 12 Years of Age or Younger

	Study 3			
	PTPs 0 to <6 yrs (N=25)		**PTPs 6 to 12 yrs (N=26)**	
	Within 48 hrs after prophylactic treatment	During prophylactic treatment[b]	Within 48 hrs after prophylactic treatment	During prophylactic treatment[b]
All Bleeds ABR Median (IQR[a] Q1; Q3)	1.9 (0.0; 4.0)	2.0 (0.0; 6.0)	0.0 (0.0; 2.0)	0.9 (0.0; 5.8)
Number of Subjects with Zero Bleeding Episodes (%)	10 (40%)		13 (50%)	

[a]IQR = Interquartile Range
[b]Independent of time of infusion

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KOVALTRY with BIO-SET®, a needleless self-contained reconstitution system, is available as a lyophilized powder in single-use glass vials, one vial per carton. The prefilled diluent syringe contains Sterile Water for Injection, USP. An administration set is also provided in the package. Available sizes:

Nominal Strength (IU)	Diluent (mL)	Kit NDC Number	Color Code
250	2.5	0026-3831-25	Blue
500	2.5	0026-3832-25	Green
1000	2.5	0026-3834-25	Red
2000	5.0	0026-3836-50	Yellow
3000	5.0	0026-3838-50	Gray

Actual Factor VIII activity in IU is stated on the label of each KOVALTRY vial.

The product vial and diluent syringe are not made with natural rubber latex.

Storage and Handling

Product as Packaged for Sale

- Store KOVALTRY at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Do not freeze. Within this period, KOVALTRY may be stored for a single period of up to 12 months at temperatures up to +25°C or 77°F.
- Record the starting date of room temperature storage on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature for 12 months, or after the expiration date on the product vial, whichever is earlier.
- Do not use KOVALTRY after the expiration date indicated on the vial.
- Protect KOVALTRY from extreme exposure to light and store the vial with the lyophilized powder in the carton prior to use.

Product After Reconstitution

- Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.
- Do not use KOVALTRY if the reconstituted solution is cloudy or has particulate matter.
- Use the administration set provided.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Hypersensitivity reactions are possible with KOVALTRY *[see Warnings and Precautions (5.1)]*. Warn patients of the early signs of hypersensitivity reactions (including tightness of the chest or throat, dizziness, mild hypotension and nausea during infusion) which can progress to anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.
- Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A *[see Warnings and Precautions (5.2)]*. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to Factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to discard all equipment, including any unused product, in an appropriate container.
- Advise patients to consult with their healthcare provider prior to travel. Advise patients to bring an adequate supply of KOVALTRY while traveling based on their current regimen of treatment.

FDA-Approved Patient Labeling

Patient Information

KOVALTRY (KOH-vahl-tree)
Antihemophilic Factor (Recombinant)

This leaflet summarizes important information about KOVALTRY with BIO-SET, a needleless self-contained reconstitution system. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about KOVALTRY. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

What is KOVALTRY?

KOVALTRY is a medicine used to replace clotting factor (Factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called "classic" hemophilia). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

KOVALTRY is used to treat and control bleeding in adults and children with hemophilia A. Your healthcare provider may give you KOVALTRY when you have surgery. KOVALTRY can reduce the number of bleeding episodes in adults and children with hemophilia A when used regularly (prophylaxis).

KOVALTRY is not used to treat von Willebrand Disease.

Who should not use KOVALTRY?

You should not use KOVALTRY if you

- are allergic to rodents (like mice and hamsters).
- are allergic to any ingredients in KOVALTRY.

What should I tell my healthcare provider before I use KOVALTRY?

- Tell your healthcare provider about all of your medical conditions.
- Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.
- Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.
- Tell your healthcare provider if you have been told that you have inhibitors to Factor VIII (because KOVALTRY may not work for you).

What are the possible side effects of KOVALTRY?

The common side effects of KOVALTRY are headache, fever and itchy rash.

Allergic reactions may occur with KOVALTRY. Call your healthcare provider right away and stop treatment if you get tightness of the chest or throat, dizziness, decrease in blood pressure, and nausea.

Your body can also make antibodies, called "inhibitors," against KOVALTRY, which may stop KOVALTRY from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII.

These are not all the possible side effects with KOVALTRY. You can ask your healthcare provider for information that is written for healthcare professionals.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

What are the KOVALTRY dosage strengths?

KOVALTRY with 2.5 mL or 5 mL Sterile Water for Injection (SWFI) comes in five different dosage strengths labeled as International Units (IU): 250 IU, 500 IU, 1000 IU, 2000 IU, and 3000 IU. The five different strengths are color-coded as follows:

Blue	250 IU with 2.5 mL SWFI
Green	500 IU with 2.5 mL SWFI
Red	1000 IU with 2.5 mL SWFI
Yellow	2000 IU with 5 mL SWFI
Gray	3000 IU with 5 mL SWFI

How do I store KOVALTRY?

Do not freeze KOVALTRY.

Store KOVALTRY at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Within this period, KOVALTRY may be stored for a period of up to 12 months at temperatures up to +25°C or 77°F.

Record the starting date of room temperature storage clearly on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The product then expires after storage at room temperature for 12 months, or after the expiration date on the product vial, whichever is earlier. Store vials in their original carton and protect them from extreme exposure to light.

Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.

Throw away any unused KOVALTRY after the expiration date.

Do not use reconstituted KOVALTRY if it is not clear.

What else should I know about KOVALTRY and hemophilia A?

Finding veins for injections may be difficult in young children. When frequent injections are required, your healthcare provider may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. These devices may result in infections.

Medicines are sometimes prescribed for purposes other than those listed here. Do not use KOVALTRY for a condition for which it is not prescribed. Do not share KOVALTRY with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about KOVALTRY. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about KOVALTRY that was written for healthcare professionals.

Instructions for Use

KOVALTRY (KOH-vahl-tree)
Antihemophilic Factor (Recombinant)

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

You should always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using KOVALTRY. If you are unsure of the procedures, please call your healthcare provider before using.

Call your healthcare provider right away if bleeding is not controlled after using KOVALTRY.

Your healthcare provider will prescribe the dose that you should take.

Your healthcare provider may need to take blood tests from time to time.

Talk to your healthcare provider before traveling. You should plan to bring enough KOVALTRY for your treatment during this time.

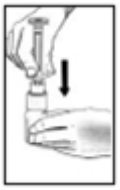
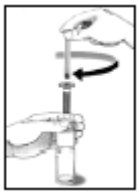
See the step-by-step instructions below for reconstituting KOVALTRY with BIO-SET. Follow the specific infusion instruction leaflet included with the infusion set provided.

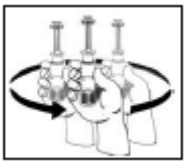
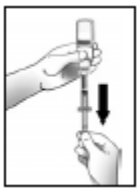
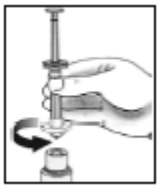
Carefully handle KOVALTRY. Dispose of all materials, including any leftover reconstituted KOVALTRY product, in an appropriate container.

Reconstitution

Always work on a clean surface and wash your hands before performing the following procedure. Use only the components for reconstitution and administration that are provided with each package of KOVALTRY. If a package is opened or damaged, do not use this component. If these components cannot be used, please contact your healthcare provider.

Prepare a clean flat surface and gather all the materials needed for the infusion.

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.	

Pooling

If the dose requires more than one vial, reconstitute each vial as described above with the diluent syringe provided. To combine the content of the vials, use a larger plastic syringe (not provided) to pool the solution into the syringe and administer as usual.

Rate of Administration

The entire dose of KOVALTRY can usually be infused within 1 to 15 minutes. Your healthcare provider will determine the rate of administration that is best for you.

Resources at Bayer available to the patient:

For Adverse Reaction Reporting, contact Bayer Medical Communications 1-888-84-BAYER (1-888-842-2937)

To receive more product information, contact KOVALTRY Customer Service 1-888-606-3780

Bayer Reimbursement HELPline 1-800-288-8374

For more information, visit www.KOVALTRY-us.com

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