EXPLORE THE POSSIBILITIES WITH CONFIDENCE

The only unmodified, full length rFVIII offering the potential for as few as 2 infusions per week[1]*

INDICATIONS

- 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 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.

SELECTED IMPORTANT SAFETY INFORMATION

- 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.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

Kovaltry®
Antihemophilic Factor (Recombinant)

*Compared to other rFVIII products.

Designed with **his future** in mind

Proven efficacy and safety in adolescents and adults with prophylaxis using as few as 2 infusions per week[1]

LEOPOLD I Trial[1,2]

Study description	◤ Multinational, open-label, prospective trial evaluating pharmacokinetics, efficacy, safety, and perioperative management of bleeding with KOVALTRY® ◤ Previously treated male patients (PTPs) aged 12 to 65 years with severe hemophilia A (<1% FVIII) (N=73) studied for 1 year
Dosing	◤ Dosing regimens were determined by the investigators to meet individual patients' needs ◤ 2x/week prophylaxis: 20-50 IU/kg (n=18) ◤ 3x/week prophylaxis: 20-50 IU/kg (n=44)
Primary efficacy endpoint	◤ Annualized bleed rate (ABR) at 12 months (n=62 for efficacy analysis)
Pharmacokinetics	◤ After a single 50 IU/kg dose of KOVALTRY®, the demonstrated half-life [mean ± standard deviation (SD)] in 26 previously treated adolescent and adult patients was:

	12 to 17 years (n=5)	≥18 years (n=21)
Chromogenic Assay	14.4 ± 5.5 hours	14.2 ± 3.5 hours
One-stage Assay	11.7 ± 1.1 hours	14.3 ± 3.7 hours

LEOPOLD=Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease.

SELECTED IMPORTANT SAFETY INFORMATION

- 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. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

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LEOPOLD I: Adolescents & adults

BAYER

ABR by dosing regimen

Dosing was investigator determined to meet individual patients' needs[1]

Patients who generally began the study with fewer bleeds and a lower percentage of target joints were selected for **2x/week prophylaxis** and experienced[1,2]	Patients who generally began the study with more bleeds and a higher percentage of target joints were selected for **3x/week prophylaxis** and experienced[1,2]
1 Median ABR (n=18) (IQR=0.0; 8.0)	**2** Median ABR (n=44) (IQR=0.5; 5.0)
Median dose: 35.0 IU/kg (range: 21-42 IU/kg)	**Median dose:** 31.1 IU/kg (range: 24-43 IU/kg)

IQR=interquartile range.

87% of bleeding episodes resolved with ≤2 infusions of KOVALTRY®[1]

0 inhibitors in **62** previously treated patients[1]

People with hemophilia A may develop inhibitors to rFVIII. People with a history of inhibitors were excluded from LEOPOLD I.[1]

SELECTED IMPORTANT SAFETY INFORMATION

- Neutralizing antibody (inhibitor) formation has occurred following administration of KOVALTRY®. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all Factor VIII products. 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.

Kovaltry®

Antihemophilic Factor (Recombinant)

LEOPOLD Kids: Designed to meet their needs

Proven efficacy and safety in previously treated children with prophylaxis using as few as 2 infusions per week[1]

LEOPOLD Kids Trial—Part A[1]

Study description

- Multinational, open-label, prospective trial evaluating the pharmacokinetics, efficacy, safety, and perioperative management of bleeding with KOVALTRY®
  - Previously treated male patients aged 0 to <6 years (n=25) and aged 6 to 12 years (n=26) with severe hemophilia A (<1% FVIII) (n=51) studied for 6 months

Dosing

- Dosing regimens were determined by the investigators to meet individual patients' needs
  - 2x/week prophylaxis: 25-50 IU/kg
  - 3x/week or every-other-day (EOD) prophylaxis: 25-50 IU/kg

Regimen	0 to <6 years	6 to 12 years
2x/week	36% (n=9)	50% (n=13)
3x/week or EOD	64% (n=16)	50% (n=13)

Primary endpoint

- Annualized number of total bleeds measured during routine prophylaxis, within 48 hours of previous prophylaxis treatment

Pharmacokinetics

- After a single 50 IU/kg dose of KOVALTRY®, the demonstrated half-life [mean ± standard deviation (SD)], using the chromogenic assay, in 18 previously treated patients 0 to 12 years of age was:

0 to <2 years (n=4)	2 to <6 years (n=5)	6 to <12 years (n=10)
9.6 ± 3.1 hours	12.2 ± 3.1 hours	12.0 ± 2.1 hours

SELECTED IMPORTANT SAFETY INFORMATION

- 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.

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ABR for total bleeds

Primary endpoint: ABR measured within 48 hours[1]	Secondary endpoint: ABR during the 6-month study[1,3]
0 Median ABR (n=51) (IQR=0.0; 4.0)	2 Median ABR (n=51) (IQR=0.0; 6.0)

2x/week prophylaxis	3x/week or EOD prophylaxis
2 Median ABR (n=21)* (range: 0-14.1)	2 Median ABR (n=30)* (range: 0-18.1)

*During the LEOPOLD Kids study, one patient was moved from a 2x/week prophylaxis regimen to a 3x/week prophylaxis regimen.

†One case of transient low titer inhibitor (0.6 BU/mL (peak titer: 1.0 BU/mL)) occurred in a 13 year old PTP after 549 EDs concurrent with an acute infection and positive IgG anticardiolipin antibodies. The Factor VIII recovery was normal (2.7 IU/dL per IU/kg), annualized bleeding rate (ABR) was zero, and no change in therapy was required.[1]

89.7% of bleeding episodes resolved with ≤2 infusions of KOVALTRY®[1]

0 inhibitors in **51** previously treated patients[1†]

No confirmed cases of neutralizing antibodies (inhibitors) to FVIII occurred.

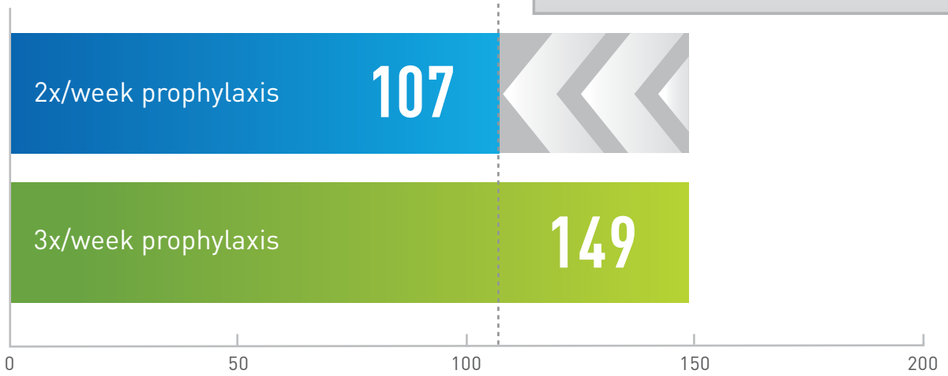
People with hemophilia A may develop inhibitors to rFVIII. People with a history of inhibitors and previously untreated children were excluded from LEOPOLD Kids—Part A.[1]

SELECTED IMPORTANT SAFETY INFORMATION

- Catheter-related infections may occur when KOVALTRY® is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.
- The most frequently reported adverse reactions in clinical trials (≥5%) were inhibitors in previously untreated patients (PUPs)/minimally treated patients (MTPs), and pyrexia, headache and rash.

Kovaltry®
Antihemophilic Factor (Recombinant)

Demonstrated **efficacy** and **safety** across all age groups of PTPs with as few as **2 infusions per week** in the LEOPOLD clinical trial program[1]



Mean number of prophylaxis infusions per patient per year[2]

Previously treated children, 0 to 12 years[1,3]

	Median ABR*
2x/week prophylaxis (n=21)	**2** (range: 0-14.1)
3x/week or EOD prophylaxis (n=30)	**2** (range: 0-18.1)

Previously treated adolescents and adults, 12 to 65 years[1]

	Median ABR*
2x/week prophylaxis (n=18)	**1** (IQR=0.0; 8.0)
3x/week prophylaxis (n=44)	**2** (IQR=0.5; 5.0)

0 inhibitors

in LEOPOLD I and LEOPOLD Kids, in 113 previously treated patients[1]

No confirmed cases of neutralizing antibodies (inhibitors) to FVIII occurred.

People with hemophilia A may develop inhibitors to rFVIII. People with previous inhibitors and previously untreated patients were excluded from LEOPOLD I and LEOPOLD Kids—Part A.[1]

*Occurring during study period.

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Kovaltry®
Antihemophilic Factor (Recombinant)

KOVALTRY®: Manufactured using **state-of-the-art** techniques[1,4]

KOVALTRY® has a FVIII **primary protein structure** that has been in use for more than **20 years**[1]

KOVALTRY® is an **unmodified, full length** rFVIII product. Post-translational modifications are similar to those of **natural FVIII**[1]

Human heat shock protein (HSP70), a chaperone protein, was introduced intracellularly to **improve proper folding of the FVIII protein**[1]

Human- and animal-derived raw materials are **not added** in the cell culture, purification, or formulation processes[1]

20-nm filtration step designed to remove potential small viruses[1]

nm=nanometer.

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The KOVALTRY® needleless reconstitution system contains[1]:

- Vial Adapter with built-in 15-micrometer filter
- 2.5 mL or 5.0 mL prefilled diluent syringe
- 25-gauge butterfly needle

Storage at room temperature (up to 77°F) for up to 1 year[1]

Store **KOVALTRY®** at 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 period of up to 12 months at temperatures up to 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.

KOVALTRY® is available in a wide range of vial sizes[1]

- Reconstitution with small diluent volumes

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TAKING THE NEXT STEP—TOGETHER

	Recommended prophylaxis dose	Regimen
Children aged ≤12 years[1]	25-50 IU/kg	2x/week, 3x/week, or EOD
Adolescents and adults[1]	20-40 IU/kg	2x/week or 3x/week

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You are encouraged to report negative side effects or quality complaints of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

References: 1. KOVALTRY® [prescribing information]. Whippany, NJ: Bayer HealthCare LLC; 2021. **2.** Data on file. Bayer HealthCare Pharmaceuticals, Inc; 2016. **3.** Ljung R, Kenet G, Mancuso ME, et al. BAY 81-8973 safety and efficacy for prophylaxis and treatment of bleeds in previously treated children with severe hemophilia A: results of the LEOPOLD Kids Trial [published online December 9, 2015]. *Haemophilia*. doi:10.1111/hae.12866. **4.** Garger S, Wu P, Regan L, et al. BAY 81-8973: a full-length, unmodified, recombinant human factor VIII product created through advanced manufacturing technologies. Poster presented at: European Association for Haemophilia and Allied Disorders 9th Annual Congress; February 2016; Malmö, Sweden.

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