Kovaltry®
Antihemophilic Factor (Recombinant)

BAYER

For your patients with hemophilia A

RECOMMEND THE COVERAGE OF KOVALTRY®

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 full Prescribing Information.

Explore dosing and PK parameters of KOVALTRY® in adults (≥18 years old)

Dosing with KOVALTRY® for routine prophylaxis[1]

Individualize the patient's dose based on clinical response

	Dose	Regimen
Adults	20–40 IU/kg	2x/week or 3x/week

PK parameters of KOVALTRY® in the LEOPOLD I trial (arithmetic mean ± SD)[1]

- PK parameters were measured using chromogenic substrate assay after a single 50 IU/kg dose of KOVALTRY® in 21 previously treated patients ≥18 years old

Parameter (unit)	**≥18 years**
AUC (IU•h/dL)	**2103.4 ± 702.8**
C_{max} (IU/dL)	**133.1 ± 20.4**
$t_{1/2}$ (h)	**14.2 ± 3.5**
MRT_{IV} (h)	**19.9 ± 4.9**
V_{SS} (dL/kg)	**0.50 ± 0.11**
CL (dL/h/kg)	**0.027 ± 0.010**

AUC=area under the curve.
CL=clearance.
C_{max}=maximum concentration.
LEOPOLD=Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease.
MRT_{IV}=mean residence time after intravenous administration.
PK=pharmacokinetics.
SD=standard deviation.
$t_{1/2}$=half-life.
V_{ss}=apparent volume of distribution at steady state.

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.

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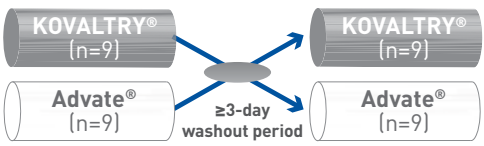
Cross-over study examining PK characteristics of KOVALTRY® and Advate® (N=18)[2]

Study summary[2,3]	
Study description	◤ The PK profiles of KOVALTRY® and Advate® were compared in a single-dose, open-label, randomized, cross-over study ◤ Previously treated male patients aged 18 to 65 years (N=18) with severe hemophilia A
Dosing	◤ Patients were randomized to a single infusion of KOVALTRY® (50 IU/kg) (n=9) or Advate® (50 IU/kg) (n=9) ◤ Patients were then crossed over to a single infusion of the other treatment, with time for washout 
PK assessment	◤ Plasma samples were collected predose and at 0.25, 0.5, 1, 3, 6, 8, 24, 30, and 48 hours postdose for PK assessment

SELECTED IMPORTANT SAFETY INFORMATION

◤ 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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PK parameters of KOVALTRY® and Advate® were studied in a single-dose, randomized, cross-over study[2]

Compared to Advate®, KOVALTRY® demonstrated, with statistical significance:

- 48% higher $AUC_{0\text{-}inf}$
- 16% longer half-life
- 30% lower clearance

Cross-over PK study results (geometric mean [%CV]) following single-dose administration (50 IU/kg) of KOVALTRY® and Advate® in 18 patients[2]

Chromogenic assay	KOVALTRY®	Advate®	*P* value
$AUC_{0\text{-}last}$ (IU•h/dL)	2200 (23.9)	1550 (27.4)	<0.0001
$AUC_{0\text{-}inf}$ (IU•h/dL)	2440 (28.5)	1650 (31.0)	<0.0001
C_{max} (IU/dL)	151 (19.9)	153 (17.1)	0.32
$t_{1/2}$ (h)	13.9 (25.1)	12.0 (23.3)	<0.0001
MRT (h)	19.2 (27.4)	15.0 (27.9)	<0.0001
CL (dL/h/kg)	0.021 (28.5)	0.030 (31.0)	<0.0001
V_{ss} (dL/kg)	0.39 (19.1)	0.46 (16.7)	<0.0001

$AUC_{0\text{-}inf}$=area under the curve from time 0 to infinity.
$AUC_{0\text{-}last}$=area under the curve from time 0 to the last data point.
CL=clearance.
C_{max}=maximum concentration
CV=coefficient of variation.
MRT=mean residence time
$t_{1/2}$=half-life.
V_{ss}=apparent volume of distribution at steady state.

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.

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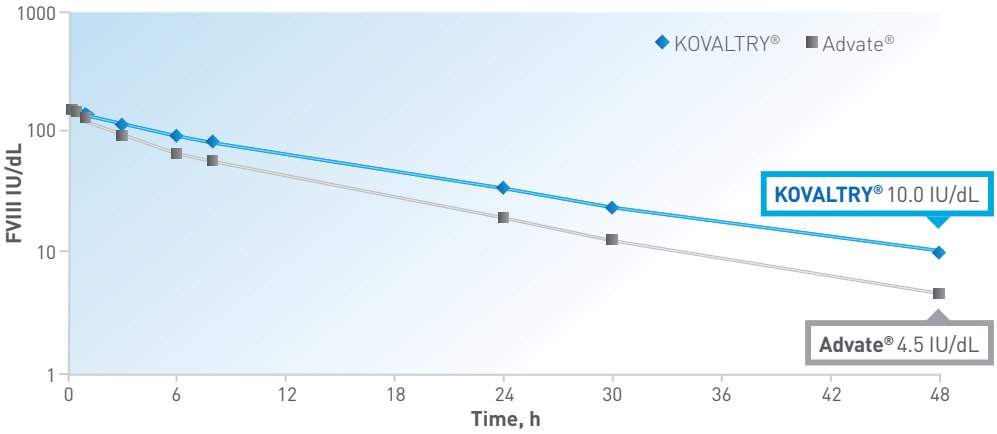
Cross-over PK Study Results: FVIII Plasma Concentrations[2,3]

- FVIII levels were 121% higher for KOVALTRY® at 48 hours compared to Advate®

FVIII levels through 48 hours (N=18)



Data are geometric means, based on chromogenic assay.

FVIII=Factor VIII.

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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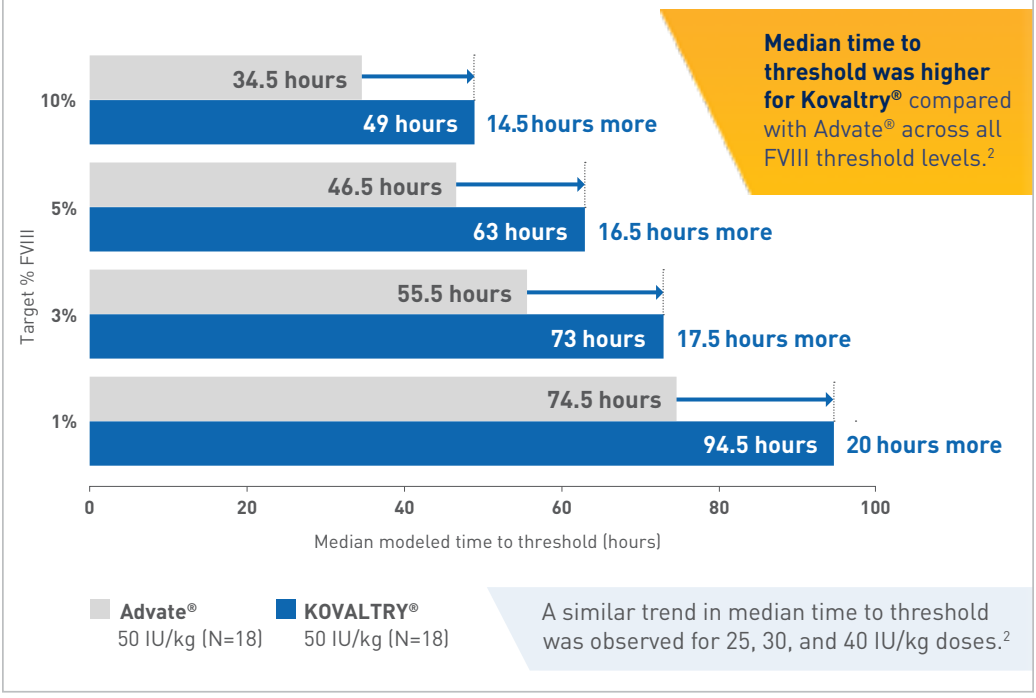
Median time to target FVIII threshold levels with KOVALTRY® vs Advate®[2]

Estimated from a population PK model (N=18)[2*]

Median Time to Target Threshold Levels[2]



Median time to threshold was higher for Kovaltry® compared with Advate® across all FVIII threshold levels.[2]

A similar trend in median time to threshold was observed for 25, 30, and 40 IU/kg doses.[2]

PK=pharmacokinetics.

*Adapted from Shah et al. A population PK model was developed based on data obtained by a one-stage assay to simulate time to reach FVIII thresholds of 1, 3, 5 and 10% FVIII.[2]

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.

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

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KOVALTRY® has your patients covered

In a cross-over study examining PK characteristics of KOVALTRY® and Advate® in adults (N=18), KOVALTRY® demonstrated:

48% higher $AUC_{0\text{-inf}}$

16% longer half-life

30% lower clearance

121% higher FVIII levels at 48 hours

and **longer median time to target FVIII threshold levels** at 10%, 5%, 3% & 1%.

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- 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
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SELECTED IMPORTANT SAFETY INFORMATION

- 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.

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

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.** Shah A, Solms A, Garmann D, et al. Improved pharmacokinetics with BAY 81-8973 versus antihemophilic factor (recombinant) plasma/albumin-free method: a randomized pharmacokinetic study in patients with severe hemophilia A [Published online December 22, 2016]. *Clin Pharmacokinet*. doi:10.1007/s40262-016-0492-2. **3.** Data on file. Bayer HealthCare Pharmaceuticals, Inc; 2016.

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