Kogenate® FS antihemophilic factor (recombinant)

Kovaltry® Antihemophilic Factor (Recombinant)

Jivi® antihemophilic factor (recombinant) PEGylated-aucl

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Post Hoc Subgroup Analysis:

Kogenate® FS* Patients Transitioned to Jivi® or Kovaltry® as Part of Clinical Trials

*Also includes patients who transitioned from Helixate FS. Kogenate FS and Helixate FS contain the same factor (active pharmaceutical ingredient and formulation).

INDICATION FOR KOGENATE FS

KOGENATE FS is an Antihemophilic Factor (Recombinant) indicated for:

- On-demand treatment and control of bleeding episodes in adults and children with hemophilia A.
- Perioperative management of bleeding in adults and children with hemophilia A.
- Routine prophylaxis to reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without pre-existing joint damage.
- Routine prophylaxis to reduce the frequency of bleeding episodes in adults with hemophilia A.

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS, KOVALTRY AND JIVI

- KOGENATE FS, KOVALTRY, or JIVI are 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. JIVI is also contraindicated in patients who have a history of hypersensitivity reactions to polyethylene glycol (PEG).

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI.

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INDICATION FOR KOVALTRY

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

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE® FS, KOVALTRY AND JIVI

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

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI.

Kogenate FS antihemophilic factor (recombinant)

Kovaltry Antihemophilic Factor (Recombinant)

Jivi antihemophilic factor (recombinant) PEGylated-aucl

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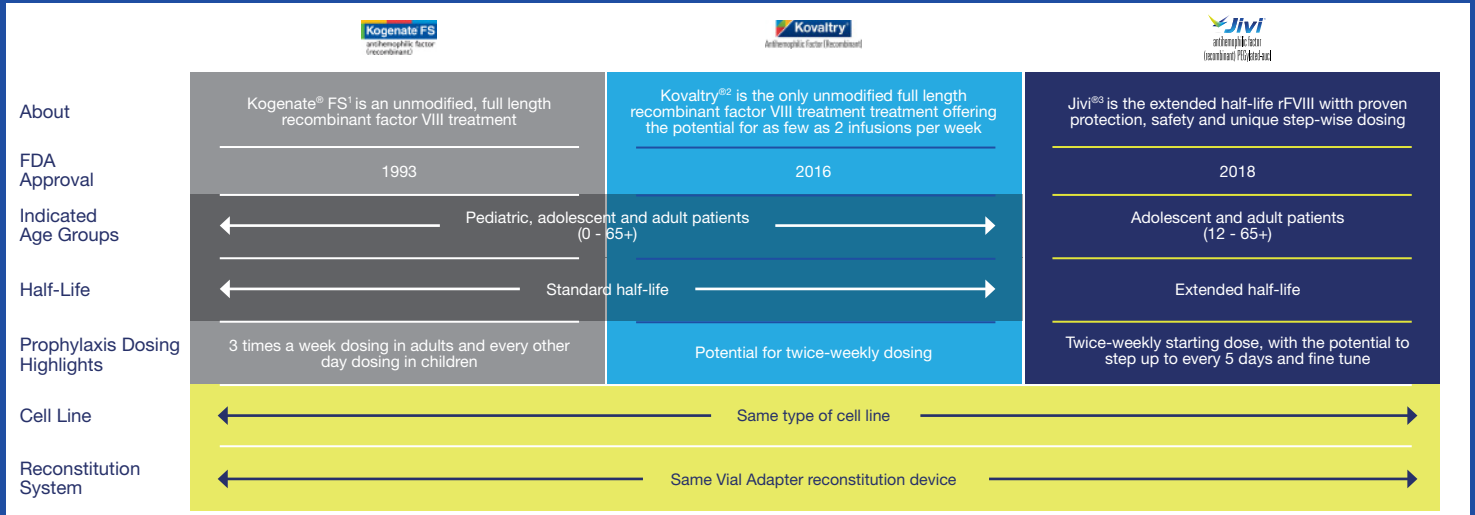
The Bayer Hemophilia A Portfolio



INDICATION FOR JIVI

JIVI antihemophilic factor (recombinant), PEGylated-aucl, is a recombinant DNA-derived, Factor VIII concentrate indicated for use in previously treated adults and adolescents (12 years of age and older) 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

LIMITATIONS OF USE FOR JIVI:

- JIVI is not indicated for use in children less than 12 years of age due to a greater risk for hypersensitivity reactions.
- JIVI is not indicated for use in previously untreated patients (PUPs).

KOGENATE FS, KOVALTRY, and JIVI are not indicated for the treatment of von Willebrand disease.

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS, KOVALTRY AND JIVI

- KOGENATE FS, KOVALTRY, or JIVI may contain trace amounts of mouse and hamster proteins. Patients treated with KOGENATE FS, KOVALTRY, or JIVI may develop hypersensitivity to these non-human mammalian proteins.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI.

Overview: Kovaltry® and Jivi® clinical trials included 61 patients previously on Kogenate® FS prophylactic therapy[2-6]

Kovaltry Clinical Trials

LEOPOLD I: Adolescents & Adults[2]

N=62

Subgroup Analysis

22 Patients previously on Kogenate® FS[4]

LEOPOLD Kids Part A: Pediatric PTPs[2]

N=51

18 Patients previously on Kogenate® FS[5]

Jivi Clinical Trial

PROTECT VIII Trial: Adolescents & Adults[3] N=110*

Subgroup Analysis

21 Patients previously on Kogenate® FS[6†]

*112 patients entered prophylactic treatment arms. Two patients in the prophylactic arms left the main study prematurely during the run-in period.
†Subgroup analysis included 3 patients 12 to < 18 years old and 18 patients 18 years or older

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS, KOVALTRY AND JIVI

- Neutralizing antibodies (inhibitors) have been reported following administration of KOGENATE FS, KOVALTRY, or JIVI predominately in previously untreated patients. 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 with an expected dose, suspect the presence of an inhibitor.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI.

Kogenate FS antihemophilic factor (recombinant)

Kovaltry Antihemophilic Factor (Recombinant)

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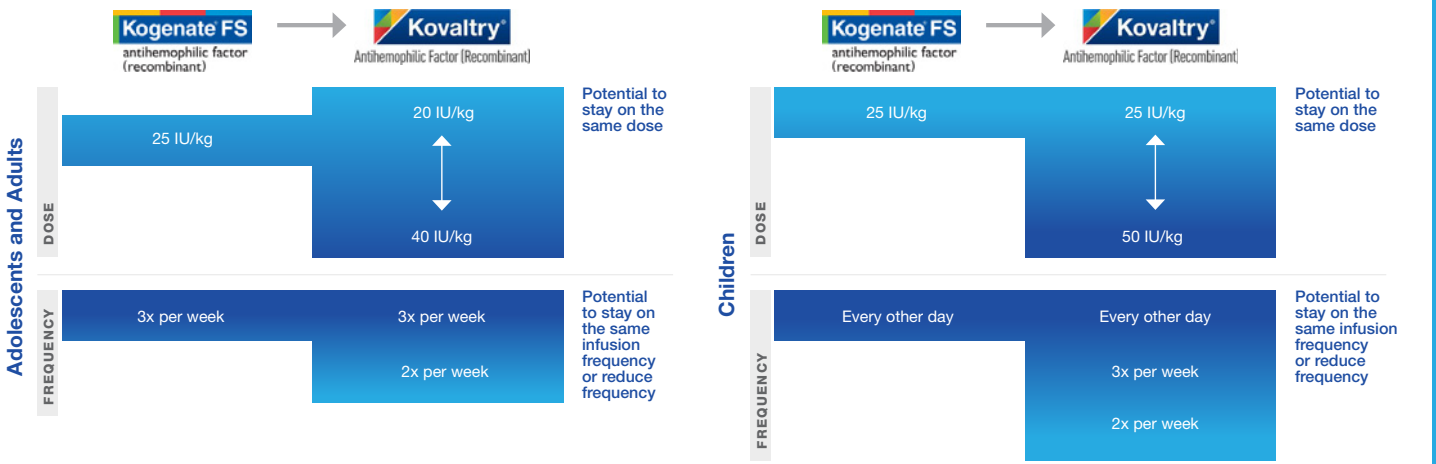
Kogenate® FS and Kovaltry®: Related at the molecular level[1,2,7]

- The Kovaltry manufacturing process begins with a cell bank derived from the Kogenate FS cell line[7]
- The Kovaltry manufacturing process incorporates advancements to the Kogenate FS manufacturing process, including[2]:
  - Removal of human- and animal-derived raw materials from the cell culture
  - Addition of a 20nm filtration step

Kovaltry offers Kogenate FS patients the opportunity to stay on the same dose and frequency[1,2]



SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS, KOVALTRY AND JIVI®

- Hypersensitivity reactions, including severe allergic reactions, are possible with KOGENATE FS, KOVALTRY, or JIVI. Monitor patients for hypersensitivity symptoms. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension and nausea. Discontinue KOGENATE FS, KOVALTRY, or JIVI if symptoms occur and seek immediate emergency treatment.
- 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 accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI ANTIHEMOPHILIC FACTOR (RECOMBINANT) PEGYLATED-AUCL.

Kogenate FS antihemophilic factor (recombinant)

Kovaltry® Antihemophilic Factor (Recombinant)

BAYER

Kovaltry®: Efficacy and safety data in adolescents and adults, including those who transitioned from Kogenate® FS[2,4,8]

LEOPOLD I Clinical Trial (N=62)

Study design
The multinational, open-label, prospective study of previously treated patients aged 12-65 years with severe hemophilia A evaluated efficacy and safety of Kovaltry 2x/week (n=18) or 3x/week (n=44) prophylaxis. The primary efficacy endpoint was annualized bleed rate (ABR) at 12 months.[2]

1 Median ABR
(n=62)
(IQR=0.0; 5.1)[8]

Median dose:
31.2 IU/kg
(range: 21-43 IU/kg)[8]

0 inhibitors
in **62** previously treated patients[2]

People with hemophilia A may develop inhibitors to rFVIII.[2‡]

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.

22 adolescent and adult Kogenate FS prophylaxis patients transitioned to Kovaltry prophylaxis as part of the LEOPOLD I clinical trial[4]

Post hoc subgroup analysis (n=22)

Kogenate FS ABR prior to study enrollment*†

2.5 Median ABR
(n=22)
(IQR=0.0; 9.0)[4]

Kovaltry ABR during study

1 Median ABR
(n=22)
(IQR=0.0; 6.8)[4]

Median dose:
35.4 IU/kg
(range: 23.99-49.26 IU/kg)[4]

0 inhibitors
in the subgroup analysis of **22** previously treated patients[2]

People with hemophilia A may develop inhibitors to rFVIII.[2‡]

There were no drug-related adverse events reported in this subgroup. during the 12 months of the main study.

Kogenate FS patients experienced **fewer annual bleeds after transitioning to Kovaltry[4†]**

IQR=interquartile range.
FVIII=factor VIII; IU=international units.
*Prior Kogenate FS or Helixate FS dose not calculated or not available.[4]
†Self-reported bleeds in prior 12 months.[4]
‡People with a history of inhibitors were excluded from LEOPOLD I[4]

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS AND KOVALTRY

In clinical trials with:

- KOGENATE FS – the most common adverse reactions (≥4%) observed were inhibitor formation in previously untreated and minimally treated patients, skin-related hypersensitivity reactions, infusion site reactions, and CVAD-associated infections.
- KOVALTRY – 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 for KOGENATE FS, KOVALTRY and JIVI® ANTIHEMOPHILIC FACTOR (RECOMBINANT) PEGYLATED-AUCL.

Kogenate FS antihemophilic factor (recombinant)

Kovaltry® Antihemophilic Factor (Recombinant)

BAYER

Kovaltry®: Efficacy and safety data in children, including those who transitioned from Kogenate® FS[2,5,9,10]

LEOPOLD Kids Clinical Trial (N=51)

Study design

The multinational, open-label study evaluated efficacy and safety of routine prophylaxis either 2 times per week, 3 times per week, or every other day with Kovaltry in previously treated male patients (≤12 years) with severe hemophilia A. The primary efficacy endpoint, ABR within 48 hours after prophylactic infusion, was 0 (0.0; 4.0).[2]

1.9 Median ABR 0-12 years (n=51) (IQR=0.0; 6.0)[2]

0–<6 years	6–12 years
Median dose: 36.4 IU/kg (range: 21-58 IU/kg)[2]	Median dose: 31.8 IU/kg (range: 22-50 IU/kg)[2]

0 inhibitors in **51** previously treated patients*

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

People with hemophilia A may develop inhibitors to rFVIII.[2†]

‡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.[2]

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.

18 pediatric Kogenate FS prophylaxis patients transitioned to Kovaltry prophylaxis as part of the LEOPOLD Kids clinical trial[5]

Post hoc subgroup analysis (n=18)

Kogenate FS ABR prior to study enrollment*

1.0 Median ABR 0-12 years (n=18) (IQR=0.0; 6.0)[5]

Kovaltry ABR during study

0.0 Median ABR 0-12 years (n=18) (IQR=0.0; 6.02)[5]

0–<6 years (n=11)	6–12 years (n=7)
Median dose: 34 IU/kg (range: 23 - 56 IU/kg)[5]	Median dose: 37.6 IU/kg (range: 23 - 47 IU/kg)[5]

0 inhibitors in the subgroup analysis of **18** previously treated patients[5]

People with hemophilia A may develop inhibitors to rFVIII.[5†]

There were no drug-related adverse events reported in this subgroup.

Kogenate FS patients experienced **fewer annual bleeds after transitioning to Kovaltry[5*]**

*Self-reported bleeds in prior 12 months.[5]

†People with a history of inhibitors and previously untreated children were excluded from LEOPOLD Kids.[5]

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS AND KOVALTRY

- 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.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI® ANTIHEMOPHILIC FACTOR (RECOMBINANT) PEGYLATED-AUCL.

Jivi
antihemophilic factor
(recombinant) PEGylated-aucl

BAYER

Jivi®: An EHL rFVIII with powerful protection from bleeds[3, 11-13]

Jivi is indicated for previously treated patients aged ≥12 years, providing:

Powerful protection from bleeds with a twice-weekly starting dose and the potential to step up to every 5 days and fine tune[2]

A **demonstrated safety profile** in previously-treated adolescents and adults[11,13]

The **potential for fewer infusions[12]:** 8/10 patients in the PROTECT VIII main study reduced dosing frequency vs their pre-study prophylaxis regimen

Unique step-wise dosing[3,15]

		For patients ≥12 years
Start simply	TWICE WEEKLY	For all prophylaxis patients: Recommended starting regimen is Jivi twice weekly (30-40 IU/kg)[2*]
Step up	EVERY 5 DAYS	Based on bleeding episodes: Less frequent dosing of Jivi every 5 days (45-60 IU/kg) can be used[2*]
Fine tune	↑↓	Based on bleeding episodes: The dosing frequency may be further adjusted up or down[2]

For more information and data from patients who participated in the Jivi extension study, and to see how Jivi's PK data compares to other EHLs, visit www.WhyJivi.com.

SELECTED IMPORTANT SAFETY INFORMATION ABOUT JIVI

- For JIVI, a clinical immune response associated with IgM anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect, has been observed primarily in patients < 6 years of age. The symptoms of the clinical immune response were transient. Anti-PEG IgM titers decreased over time to undetectable levels. No immunoglobulin class switching was observed. In case of clinical suspicion of loss of drug effect, conduct testing for Factor VIII inhibitors and Factor VIII recovery.
- For JIVI, a low post-infusion Factor VIII level in the absence of detectable Factor VIII inhibitors indicates that loss of drug effect is likely due to anti PEG antibodies. Discontinue JIVI and switch patients to a previously effective Factor VIII product.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE® ANTIHEMOPHILIC FACTOR (RECOMBINANT), KOVALTRY® ANTIHEMOPHILIC FACTOR (RECOMBINANT) and JIVI.

Kogenate FS antihemophilic factor (recombinant)

Jivi antihemophilic factor (recombinant) PEGylated-aucl

BAYER

Jivi®: Efficacy and safety data in adolescents and adults, including those who transitioned from Kogenate® FS[3,6,14]

PROTECT VIII Clinical Trial (N=110)

Study design
110 patients completed a 10-week run-in period where they received 25 IU/kg twice weekly. They were then assigned or randomized to a treatment arm based on bleeding tendency. Among patients with low bleeding tendencies, 11 received 30-40 IU/kg twice weekly and 43 patients received 45-60 IU/kg every 5 days for 26 weeks. 13 patients with high bleeding tendencies received 30-40 IU/kg twice weekly for 26 weeks.[3]

		Twice-weekly		Every 5 days	Combined[14]
Bleeding Tendency[3]		LOW* (n=11)	HIGH† (n=13)	LOW* (n=43)	n=67
Total ABR (weeks 10-36)[2]	Median ABR (Q1;Q3)[3]	1.9 (0.0; 5.2)	4.1 (2.0; 10.6)	1.9 (0.0; 4.2)	2.1 (0.0; 5.8)
	Mean (SD)[3]	2.2 (2.7)	7.2¶ (7.5)	3.3 (4.3)	3.9 (5.1)
Jivi Median (Range) Prophylaxis Dose/ Infusion, IU/kg[3]		30.6 (29-41)	39.2 (33-42)	45.3 (39-58)	

0 ZERO inhibitors in the completed study‡[11,12]
‡Factor VIII inhibitor (1.7 BU/mL) was reported in one previously treated adult subject. Repeat testing did not confirm the presence of a Factor VIII inhibitor.[2]

- The common side effects of Jivi are headache, cough, nausea, and fever.
- Allergic reactions occurred in 2 patients. In 1 patient, the allergic reaction was related to polyethylene glycol (PEG), a component of Jivi

21 adolescent and adult Kogenate FS patients (12 years of age or older) transitioned to Jivi prophylaxis as part of the 26 week Jivi Clinical study[6]

Post hoc subgroup analysis (n=21)

~67% of the subgroup were on an every-5-day Jivi regimen

	Kogenate FS ABR prior to study enrollment	Jivi ABR During Study
Median ABR (Q1;Q3)[6]	9 (1.0; 15.0)	2.1 (0.0; 10.0)
Mean (SD)[6]	10.5 (12.3)	5.2 (7.2)

Kogenate FS patients experienced **fewer annual bleeds after transitioning to Jivi**[6§]

	Twice-weekly		Every 5 days
Bleeding Tendency[6]	LOW (n=3)	HIGH (n=4)	LOW (n=14)
Jivi Median (Range) Prophylaxis Dose/Infusion, IU/kg[6]	31.4 (29 - 33)	41.2 (37 - 42)	45.4 (41 - 54)

0 ZERO inhibitors in the subgroup analysis of 21 previously treated patients[6]

- A drug-related adverse event was reported in one patient. There were no serious drug related adverse events.

ABR, annualized bleed rate.
*Patients with 0 or 1 spontaneous bleed (defined as a joint or muscle bleed and no identified trauma) during weeks 1-10 of the main study.[11]
†Patients with 2 or more spontaneous bleeds (defined as joint or muscle bleeds and no identified trauma) during weeks 1-10 of the main study.[11]
‡June 2014 data cutoff
§Self-reported bleeds in prior 12 months.[6]
¶n=9/13 of these patients were on prior prophylaxis and had a mean number total ABR of 17.4 before entering the main study.[3]

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS AND JIVI

In clinical trials with:

- KOGENATE FS – the most common adverse reactions (≥4%) observed were inhibitor formation in previously untreated and minimally treated patients, skin-related hypersensitivity reactions, infusion site reactions, and CVAD-associated infections.
- JIVI – the most frequently (≥5%) reported adverse reactions in previously treated patients (PTPs) ≥12 years of age were headache, cough, nausea, and fever.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY® ANTIHEMOPHILIC FACTOR (RECOMBINANT) and JIVI.

Kogenate FS antihemophilic factor (recombinant)

Kovaltry® Antihemophilic Factor (Recombinant)

Jivi® antihemophilic factor (recombinant) PEGylated-aucl

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Summary

Kovaltry® offers patients currently on Kogenate® FS...

- A cell bank derived from the Kogenate FS cell line[7]
- Advancements to the Kogenate FS manufacturing process, including[2]:
  - Removal of human- and animal-derived raw materials from the cell culture
  - Addition of 20nm filtration step
- The potential to stay on the same dose and frequency[2]

Jivi® offers adolescent and adult patients currently on Kogenate FS...

- **Powerful protection from bleeds** with a twice-weekly starting dose and the potential to step up to every 5 days and fine tune[3]
- The **potential for fewer infusions**[12]:
  - 8/10 patients in the PROTECT VIII main study reduced dosing frequency vs their pre-study prophylaxis regimen

In a post hoc analysis, Kogenate FS patients who transitioned to Kovaltry experienced[4,5]:

- A reduction in ABR*
- Zero inhibitors

In a post hoc analysis, Kogenate FS patients who transitioned to Jivi experienced[6]:

- A reduction in ABR*
- Zero inhibitors

~67% of Kogenate patients enrolled in the Jivi clinical trial were on an every-5-day-regimen

*Self-reported bleeds in prior 12 months.[4,5,6]

1. Kogenate Prescribing Information. Bayer HealthCare LLC, Whippany, NJ. 2. Kovaltry Prescribing Information. Bayer HealthCare LLC, Whippany, NJ; 2021. 3. Jivi [antihemophilic factor (recombinant), PEGylated-aucl] Prescribing Information. Bayer HealthCare LLC, Whippany, NJ; 2018. 4. Data on file. Leopold I (12954) prior Kogenate FS/Helixate FS cohort. Bayer HealthCare LLC, Whippany, NJ. 5. Data on file. LEOPOLD Kids Subgroup Analysis. Bayer HealthCare LLC, Whippany, NJ. 6. Data on file. Jivi Protect VIII Subgroup Analysis. Bayer HealthCare LLC, Whippany, NJ. 7. Data on File. Kovaltry Summary Basis for Regulatory Action. Bayer HealthCare LLC, Whippany, NJ; 2016. 8. Saxena K, Lalezari S, Oldenburg J, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. Haemophilia. 2016;22(5):706-712. 9. NCT01311648. https://clinicaltrials. gov. Accessed July 11, 2017. 10. Ljung R, et al. Haemophilia. 2016;22(3):354-360. 11. Reding MT et al. J Thromb Haemost 2017;15:411-419. 12. Kerlin BA et al. Poster P153. Presented at the 4th Biennial Summit of the Thrombosis & Haemostasis Societies of North America. March 8-10, 2018, San Diego, California. 13. Lalezari S et al. Haemophilia 2019;25:1011-1019. 14. Data on file. Jivi Protect VIII Clinical Trial Combined Table. Bayer HealthCareLLC, Whippany, NJ. 15.Data on file. Tx Review 0918, Bayer; 2018.

SELECTED IMPORTANT SAFETY INFORMATION ABOUT KOGENATE FS, KOVALTRY AND JIVI

- Neutralizing antibodies (inhibitors) have been reported following administration of KOGENATE FS, KOVALTRY, or JIVI predominately in previously untreated patients. 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 with an expected dose, suspect the presence of an inhibitor.

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

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information for KOGENATE FS, KOVALTRY and JIVI.