For your patients 12 years of age or older with Hemophilia A

Recommend the coverage of Jivi®

INDICATIONS

- 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:
  - 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).
  - Jivi is not indicated for the treatment of von Willebrand disease.

SELECTED IMPORTANT SAFETY INFORMATION

- Jivi is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, polyethylene glycol (PEG), mouse or hamster proteins, or other constituents of the product.

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Jivi®
antihemophilic factor (recombinant) PEGylated-aucl
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Explore dosing and...

Dosing with Jivi® for routine prophylaxis

Indicated for previously treated patients ≥12 years of age[1]

Start simply	TWICE **WEEKLY**	**For all prophylaxis patients:** Recommended starting regimen is Jivi® **twice weekly** (30–40 IU/kg)[1]
Step up	EVERY **5 DAYS**	**Based on bleeding episodes:** Less frequent dosing of Jivi® **every 5 days** (45–60 IU/kg) can be used[1]
Fine tune		**Based on bleeding episodes:** The dosing frequency may be further **adjusted up or down**[1]

SELECTED IMPORTANT SAFETY INFORMATION

- Hypersensitivity reactions, including severe allergic reactions, have occurred with 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. If hypersensitivity reactions occur, immediately discontinue administration and initiate appropriate treatment.
- Jivi 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 Jivi® in patients ≥12 years of age[1]

PK parameters of Jivi® in the PROTECT VIII trial (arithmetic mean ± SD)[1]

- Measured following a single dose (25 IU/kg and 60 IU/kg)[1]

	Chromogenic assay		One-stage assay	
PK parameters (unit)	25 IU/kg n=7	60 IU/kg[a] n=29	25 IU/kg n=7	60 IU/kg[a] n=29
AUC (IU*h/dL)	1640 ± 550	4060 ± 1420	1640 ± 660	4150 ± 1060
C_{max} (IU/dL)	64.2 ± 9.2	167 ± 30	69.4 ± 11.3	213 ± 71
$t_{½}$ (h)	18.6 ± 4.6	17.9 ± 4.0	21.4 ± 13.1	17.4 ± 3.8
MRT_{IV} (h)	26.7 ± 6.6	25.8 ± 5.9	29.0 ± 14.0	24.5 ± 5.4
V_{ss} (mL/kg)	42.8 ± 5.0	39.4 ± 6.3	44.7 ± 5.4	36.0 ± 6.5
CL (mL/h)	142 ± 33	121 ± 53	146 ± 44	114 ± 41
CL (mL/h/kg)	1.68 ± 0.39	1.63 ± 0.52	1.74 ± 0.54	1.52 ± 0.38
Recovery [(IU/dL)/(IU/kg)]	2.13 ± 0.47	2.53 ± 0.43[b]	2.21 ± 0.55	3.25 ± 0.84[b]

[a]Combined data from Phase 1 and Phase 2/3 studies.

[b]Recovery value could not be calculated for one subject.

PK: pharmacokinetic; SD: standard deviation; 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.

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- Hypersensitivity reactions may also be related to antibodies against polyethylene glycol (PEG).
- Neutralizing antibody (inhibitor) formation can occur following administration of Jivi. 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).

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Crossover study examining PK characteristics of Jivi® and Eloctate® (N=18)[2]*

Study description	The PK profiles of Jivi® and Eloctate® were compared in a randomized, open-label, single-dose, crossover study with a washout period between. • Previously treated male patients aged 18-65 years with severe hemophilia A with no history of FVIII inhibitors • Primary endpoint: $AUC_{(0\text{-}t_{last})}$ based on one-stage clotting assay
Dosing	
PK assessment	PK samples were collected predose, and at 11 time points: 0.25, 0.5, 1, 3, 6, 8, 24, 48, 72, 96, and 120 hours after infusion.

AUC, area under the curve (from time zero to last data point)†; PK, pharmacokinetic.

*Adapted from Shah et al.

†Area under the curve is the total amount of a drug that reaches the bloodstream, measured by plasma concentration, over time.[3]

SELECTED IMPORTANT SAFETY INFORMATION

- 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. 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.
- The most frequently (≥5%) reported adverse reactions in clinical trials in previously treated patients (PTPs) ≥12 years of age were headache, cough, nausea, and fever.

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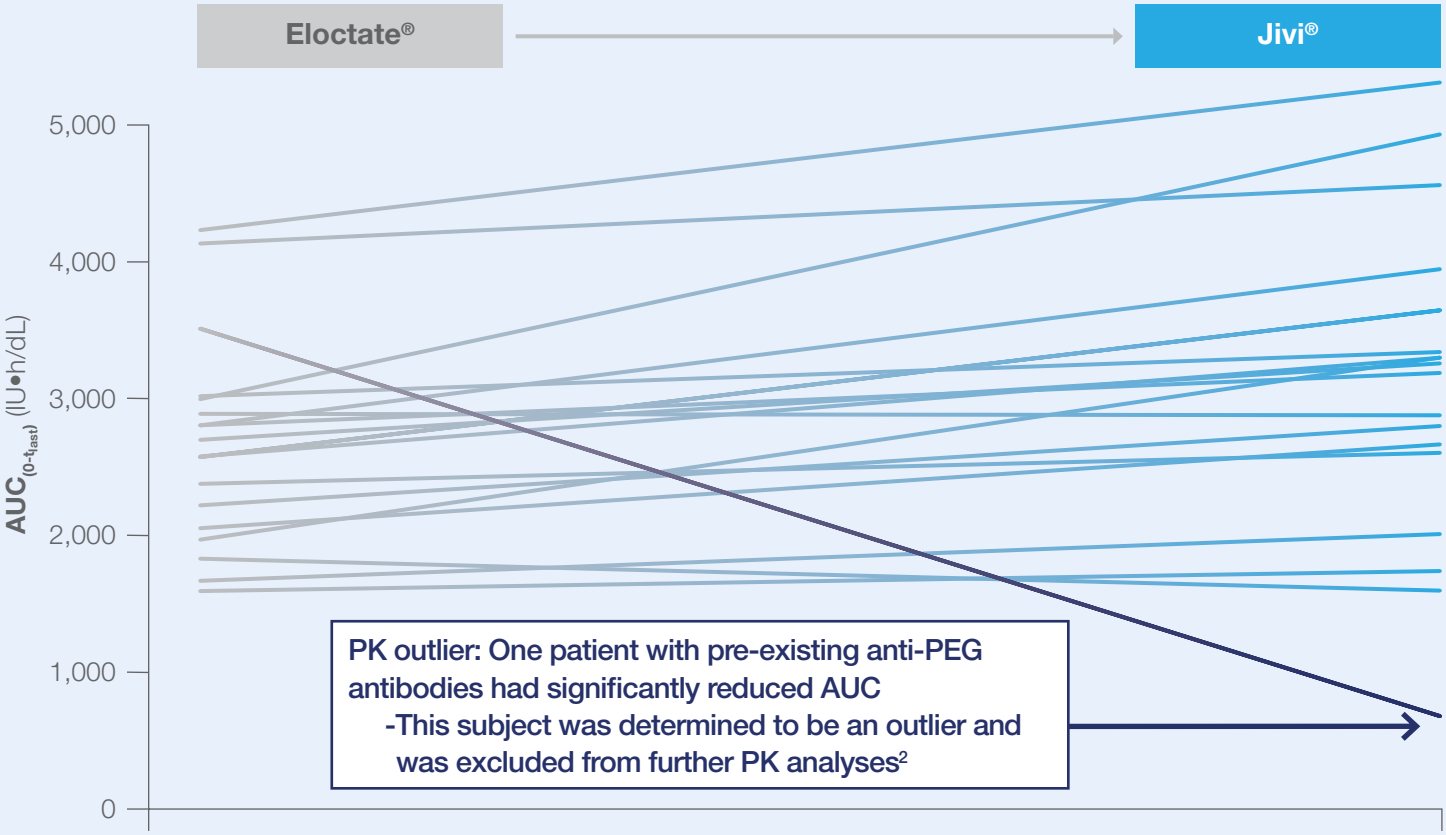
Jivi® AUC compared to Eloctate® in 18 patients[2]*



- The pre-specified criteria for non-inferiority of Jivi® vs Eloctate® were met
- Superiority criteria of the Jivi®:Eloctate® ratio were not met (95% CI 0.84–1.46; *P*=0.46)

PEG, polyethylene glycol.

*Adapted from Shah et al.

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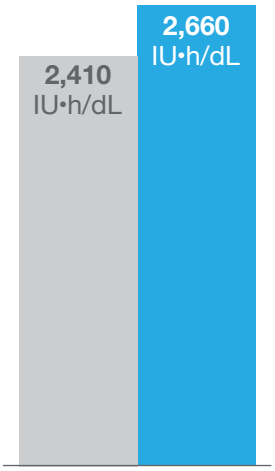
Comparative PK results for Jivi® vs Eloctate®[2]

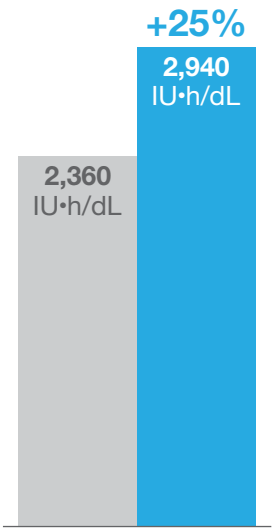
Compared with Eloctate, Jivi demonstrated statistically significantly (N=17)*:

MEAN AUC[2]
***p*=0.46**
(N=18)



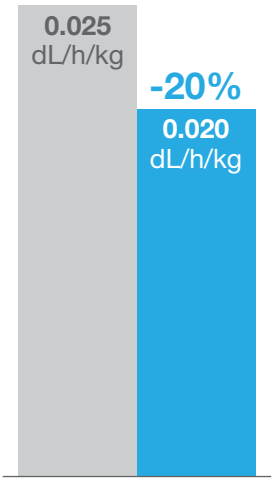
Mean ratio‖ (90% CI):
1.10 (0.88–1.39)

HIGHER MEAN AUC[2†]
***p*=0.0001**



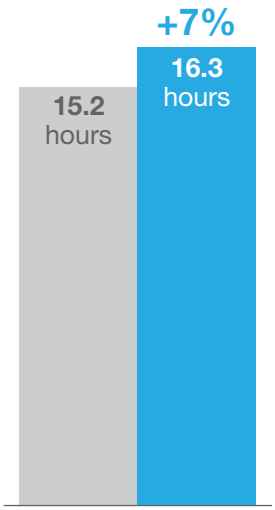
Mean ratio‖ (95% CI):
1.25 (1.14–1.37)

LOWER MEAN CLEARANCE[2‡]
***p*=0.0001**



Mean ratio‖ (95% CI):
0.80 (0.72–0.87)

LONGER MEAN TERMINAL HALF-LIFE[2§]
***p*<0.05**



Mean ratio‖ (95% CI):
1.07 (1.00–1.15)¶

Eloctate® **Jivi®**

AUC, area under the curve (from time zero to last data point); CI, confidence interval; PK, pharmacokinetic.

*Excluding outlier patient, who had anti-PEG antibodies.[2]

†Area under the curve is the total amount of a drug that reaches the bloodstream, measured by plasma concentration over time.[3]

‡Clearance is the time it takes for a drug to be completely eliminated from the body.[4]

§Half-life is the time it takes for the amount of a drug in the blood to decrease by one half.[5]

‖Geometric least squares.[2]

¶Actual 95% confidence interval is 1.0026 - 1.1516.[6]

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- Jivi 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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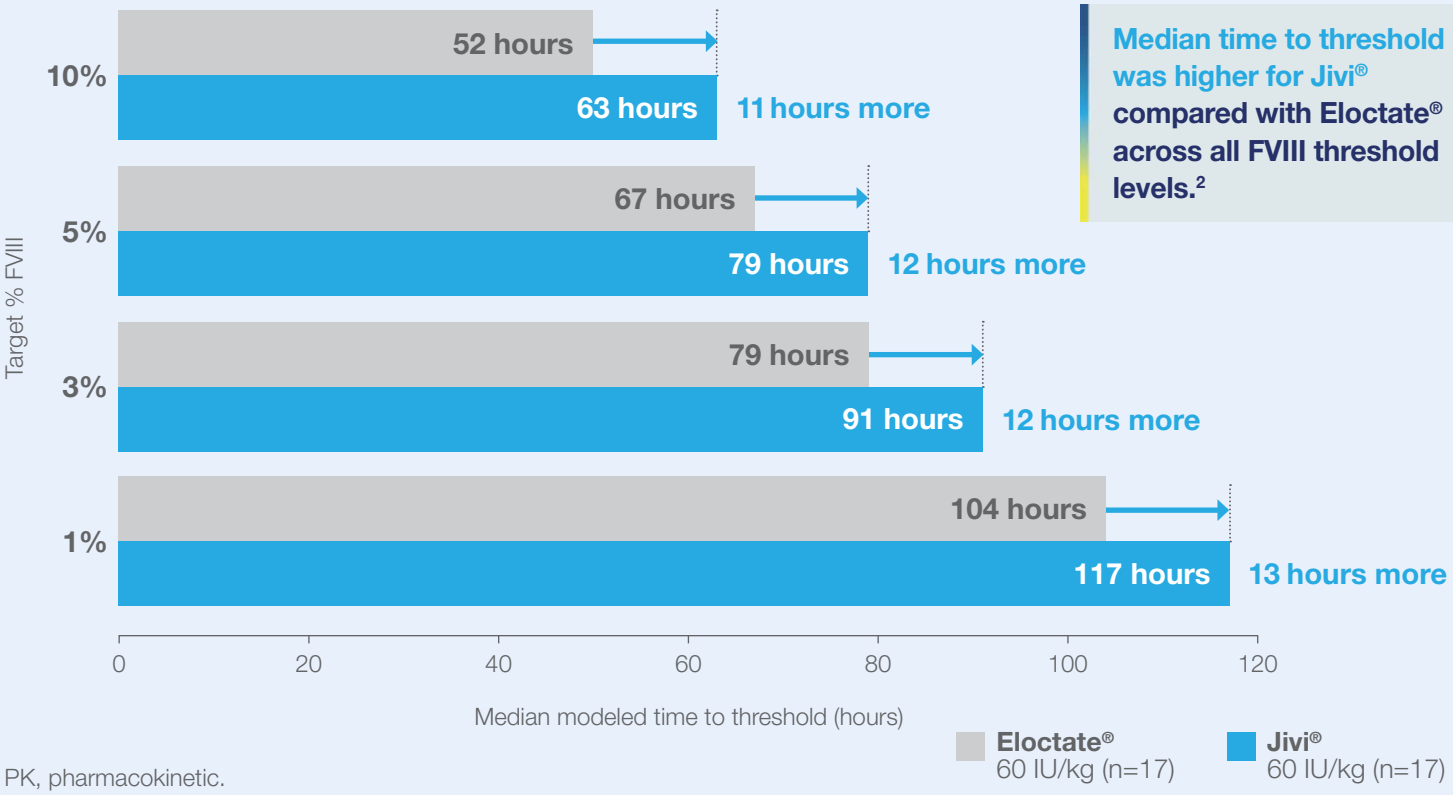
Median time to target FVIII threshold levels with Jivi® vs Eloctate®[2]

Estimated from a population PK model (excluding outlier, N=17)[2]*



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

PK, pharmacokinetic.

*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]

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Compared with Eloctate®, Jivi® demonstrated statistically significantly (N=17)*:

25%
Higher Mean AUC[2†]

20%
Lower Mean Clearance[2‡]

7% Longer Mean Terminal
Half-life[2§]

Longer median time
to target FVIII threshold levels (10,5,3,1%)[2]

For N=18 patients, including the PK outlier patient, Jivi® demonstrated non-inferiority to Eloctate® for $AUC_{(0\text{-}t_{last})}$

AUC, Area under the curve.

*Excluding outlier patient, who had anti-PEG antibodies.[2]

†Area under the curve is the total amount of a drug that reaches the bloodstream, measured by plasma concentration over time.[3]

‡Clearance is the time it takes for a drug to be completely eliminated from the body.[4]

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References: 1. Jivi® Prescribing Information. Whippany, NJ: Bayer LLC; 2018. **2.** Shah A, Solms A, Wiegmann S, et al. Direct comparison of two extended-half-life recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A. *Ann Hematol.* 2019;1-10. https://link.springer.com/article/10.1007%2Fs00277-019-03747-2. Published June 24, 2019. Accessed June 25, 2019. **3.** Anderson PL. The ABCs of pharmacokinetics. http://www.thebody.com/content/art875.html. Accessed April 2018. **4.** Dhillon S, Gill K. Basic pharmacokinetics. In: Dhillon S, Kostrzewski A, eds. *Clinical Pharmacokinetics*. London, UK: Pharmaceutical Press; 2006. **5.** Ratain MJ, Plunkett WK Jr. Principles of pharmacokinetics. In: Kufe DW, Pollock RE, Weichselbaum RR, et al, eds. *Holland-Frei Cancer Medicine*. 6th ed. Hamilton, Ontario: BC Decker; 2003. **6.** Jivi vs Eloctate PK Confidence Interval Data Table from CSR. Bayer; 2019.

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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.

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