
## ADVATE Important Information

### What is ADVATE?

- ADVATE 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).
- ADVATE is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A. Your healthcare provider (HCP) may give you ADVATE when you have surgery.
- ADVATE can reduce the number of bleeding episodes in adults and children (0-16 years) when used regularly (prophylaxis).

ADVATE is not used to treat von Willebrand disease.

**Please see ADVATE Important Risk Information located throughout this brochure and Important Facts about ADVATE at the end of the brochure.**

## SELECTED IMPORTANT RISK INFORMATION

### Who should not use ADVATE?

Do not use ADVATE if you:

- Are allergic to mice or hamsters.
- Are allergic to any ingredients in ADVATE.

Tell your HCP if you are pregnant or breastfeeding because ADVATE may not be right for you.

ADVATE
[Antihemophilic Factor (Recombinant)]

REAL LIFE. REAL BLEED PROTECTION.*

Takeda

# Preventing Bleeds Is Key

## Prophylaxis may help you prevent or reduce the frequency of bleeds[1]


of Patients Experienced
**Zero Bleeds**
during 1 year on prophylaxis[1]
(n=22 in the per-protocol group of 53)

**44 Bleeds**
(IQR, 20.8)
**Reduced To**
**1 Bleed**
(IQR, 4.1)

**98%**
Reduction in bleeds[1]

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- In an open-label, randomized, controlled clinical study of the efficacy of ADVATE use in 2 prophylactic treatment regimens compared to that of on-demand treatment, 53 previously treated patients (PTPs) with severe to moderately severe hemophilia A were analyzed in the per-protocol group[1,2]
- Patients were initially treated for 6 months of on-demand therapy and then randomized to 12 months of either a standard prophylaxis regimen (20–40 IU/kg every 48 hours) or a pharmacokinetic-driven prophylaxis regimen (20–80 IU/kg every 72 hours)[1,2]
- ABRs for the two prophylaxis regimens were comparable[1]
- In a clinical trial, 0 bleeds in 42% of patients during 1 year on the prophylaxis (n=22 in the per-protocol group of 53).[1] Per-protocol: subjects who had >90% of the predicted number of infusions and no major protocol deviations[1]
- In a clinical trial, 98% reduction in median ABR from 44 to 1 when patients switched from on-demand to prophylaxis[1,2]

## SELECTED IMPORTANT RISK INFORMATION (continued)

### What should I tell my HCP before using ADVATE?

Tell your HCP if you:

- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to mice or hamsters.
- Are breastfeeding. It is not known if ADVATE passes into your milk and if it can harm your baby.
- Are or become pregnant. It is not known if ADVATE may harm your unborn baby.
- Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

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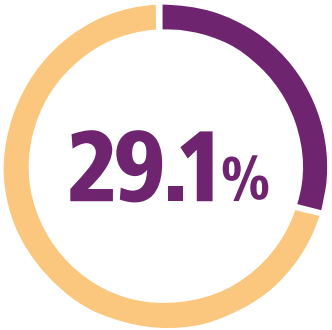
# Established safety profile[1,3,4]


Incidence of Inhibitors
**in PTPs**
1/276 Patients
(95% CI: 0.009%–2.002%)[3†]




Incidence of Inhibitors
**in PTPs and MTPs**
16/55 Patients
(95% CI: 17.1%–41.1%)[1,4‡]

[†]Low risk of inhibitor development in PTPs demonstrated in 8 clinical studies; 0.36% incidence of inhibitors in 276 PTPs (95% CI: 0.009%–2.002%).[3] One PTP developed a nonpersistent, low-titer inhibitor: there was 1 additional case of a possible low-titer factor VIII inhibitor, which was unconfirmed, was unaccompanied by symptoms of inhibitor presence, and disappeared at the subject's subsequent test.[2]

[‡]In a study investigating immunogenicity, results showed a 29.1% incidence of inhibitors in PUPs and MTPs (16/55).[1,4]

The safety of ADVATE was evaluated in 8 studies in 276 PTPs with moderately severe to severe hemophilia A. PTPs were defined as having ≥50 or ≥150 exposure days (EDs) to FVIII products, depending on the study. In this analysis, PTPs were defined as patients with ≥50 EDs. For PTP inhibitor incidence, all PTPs with ≥10 consecutive EDs (N=276) during the course of individual studies were included in the analysis. EDs were defined as calendar days on which rAHF-PFM was administered.[3]

The safety of ADVATE was evaluated in a multicenter, open-label clinical study of 55 previously untreated patients (PUPs) and minimally treated patients (MTPs) <6 years of age with severe (FVIII level <1%) or moderately severe (FVIII level 1%–2%) hemophilia A determined at baseline. PUPs and MTPs were defined as having had up to 3 exposures to a factor VIII product at time of enrollment. Patients were followed for 75 exposure days or 3 years, whichever occurred first. The primary safety endpoint was the percentage of subjects who developed an inhibitor to FVIII.[1,4]

***In clinical trials, ADVATE demonstrated the ability to help patients prevent bleeding episodes using a prophylaxis regimen.**

## SELECTED IMPORTANT RISK INFORMATION (continued)

### What important information do I need to know about ADVATE?

- You can have an allergic reaction to ADVATE. Call your HCP right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.
- Do not attempt to infuse yourself with ADVATE unless you have been taught by your HCP or hemophilia center.

### What else should I know about ADVATE and Hemophilia A?

- Your body may form inhibitors to factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop ADVATE from working properly. Talk with your HCP to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

**Please see ADVATE Important Risk Information located throughout this brochure and Important Facts about ADVATE at the end of the brochure.**

# Access Personalization and Support

## With the myPKFiT® for ADVATE® Patients Mobile App

In the US, myPKFiT is intended to be used with ADVATE patients who are 16 years of age or older with a body weight of 45 kg or greater.

**The myPKFiT for ADVATE Mobile App** can help you stay engaged with your personalized treatment plan and allows you to share important data with your doctor.[5]

**Plan** activities and events based on estimated FVIII levels[1]

**Track** infusions and bleeds with a few taps[1]

**Connect** with your healthcare professional via secure data export[1]

## Proven clinical experience

**15+ Years of Real-World Experience**
Third-generation full-length molecule, similar to the factor VIII that occurs naturally in the body[6]

**Extensively Studied**
Evidence spanning over 15 years from 15 prospective studies[6,7]

**The Most Widely Used FVIII Product†**
With 33 billion International Units (IUs) sold worldwide[7]

†Based on units sold, as of July 2018.

### myPKFiT® for ADVATE Patients Mobile Application

#### Intended Use

- The myPKFiT for Patients Mobile Application ("myPKFiT Mobile App") is intended for use by patients with hemophilia A being treated with ADVATE [Antihemophilic Factor (Recombinant)] who are 16 years of age or older with a body weight of 45 kg or higher, and their caregivers.
- The myPKFiT Mobile App is designed to make it convenient for you to record your infusion and bleed events, track your estimated Factor VIII levels following a prophylactic infusion, and export the data for review by your health care provider ("HCP").
- Your HCP can use the myPKFiT software to generate ADVATE dosage amount and frequency recommendations for routine prophylaxis using your age, body weight information, and laboratory tests that measure your Factor VIII clotting activity. Using myPKFiT software, HCPs can evaluate various prophylaxis dose regimens tailored to your individual needs and treatment plan.
- myPKFiT Mobile App should only be used by hemophilia A patients treated with ADVATE, as per the ADVATE Prescribing Information.
- myPKFiT Mobile App is not indicated for use by patients with von Willebrand disease. myPKFiT Mobile App should not be used by patients who have developed inhibitors to Factor VIII products.

**myPKFiT for Patients Mobile Application is Rx only. For safe and proper use of the myPKFiT Mobile App, please refer to the complete instructions for use in the User Manual.**

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# Support throughout the treatment journey

## FREEDOM OF CHOICE™ Program



**FREE-TRIAL PROGRAM**

You may be eligible to receive 6 free-trial doses of ADVATE with the FREEDOM OF CHOICE trial program. The free trial program is for new patients only. Participants must receive consultation and approval from their healthcare provider. For more information, visit www.advate.com.

## Takeda's CoPay Assistance Program



For eligible patients, learn how our CoPay Assistance Program may cover out-of-pocket expenses related to treatment that requires a co-pay, up to the program maximum.

## Hematology Support Center



Hematology Support Center (HSC) is a dedicated team that helps patients who have been prescribed Takeda Hematology products with information, guidance, and resources regarding their treatment. Learn more at **888-229-8379** Monday–Friday 8:30AM–8:00PM ET or online at **www.hematologysupport.com**.



## ADVATE with BAXJECT III® Instructions

Learn how to reconstitute your medication, including easy one-step activation for reconstituting the ADVATE in a BAXJECT III system.[1] Visit the ADVATE channel on www.YouTube.com to access the instructional videos. You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center.

***In clinical trials, ADVATE demonstrated the ability to help patients prevent bleeding episodes using a prophylaxis regimen.**

## SELECTED IMPORTANT RISK INFORMATION (continued)

### What are possible side effects of ADVATE?

- Side effects that have been reported with ADVATE include: cough, headache, joint swelling/aching, sore throat, fever, itching, unusual taste, dizziness, hematoma, abdominal pain, hot flashes, swelling of legs, diarrhea, chills, runny nose/congestion, nausea/vomiting, sweating, and rash. Tell your HCP about any side effects that bother you or do not go away or if your bleeding does not stop after taking ADVATE.

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

**For additional safety information, please see Important Facts about ADVATE on the following page and discuss with your HCP. For full Prescribing Information, visit www.ADVATE.com.**

**Please see ADVATE Important Risk Information located throughout this brochure and Important Facts about ADVATE at the end of the brochure.**

ADVATE
[Antihemophilic Factor (Recombinant)]

## Important facts about ADVATE [Antihemophilic Factor (Recombinant)]

This leaflet summarizes important information about ADVATE. 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 ADVATE. If you have any questions after reading this, ask your healthcare provider.

### What is the most important information I need to know about ADVATE?

Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.

You must carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing ADVATE so that your treatment will work best for you.

### What is ADVATE?

ADVATE 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). The product does not contain plasma or albumin. Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

ADVATE is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A.

Your healthcare provider may give you ADVATE when you have surgery. ADVATE can reduce the number of bleeding episodes in adults and children (0-16 years) when used regularly (prophylaxis).

ADVATE is not used to treat von Willebrand disease.

### Who should not use ADVATE?

You should not use ADVATE if you:

- Are allergic to mice or hamsters.
- Are allergic to any ingredients in ADVATE.

Tell your healthcare provider if you are pregnant or breastfeeding because ADVATE may not be right for you.

### How should I use ADVATE?

ADVATE is given directly into the bloodstream.

You may infuse ADVATE at a hemophilia treatment center, at your healthcare provider's office or in your home. You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center. Many people with hemophilia A learn to infuse their ADVATE by themselves or with the help of a family member.

Your healthcare provider will tell you how much ADVATE to use based on your weight, the severity of your hemophilia A, and where you are bleeding.

You may have to have blood tests done after getting ADVATE to be sure that your blood level of factor VIII is high enough to clot your blood.

Call your healthcare provider right away if your bleeding does not stop after taking ADVATE.

### What should I tell my healthcare provider before I use ADVATE?

You should tell your healthcare provider if you:

- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to mice or hamsters.
- Are breastfeeding. It is not known if ADVATE passes into your milk and if it can harm your baby.
- Are pregnant or planning to become pregnant. It is not known if ADVATE may harm your unborn baby.
- Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

### What are the possible side effects of ADVATE?

You can have an allergic reaction to ADVATE.

Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.

Side effects that have been reported with ADVATE include:

| | | |
|---|---|---|
| cough | headache | joint swelling/aching |
| sore throat | fever | itching |
| unusual taste | dizziness | hematoma |
| abdominal pain | hot flashes | swelling of legs |
| diarrhea | chills | runny nose/congestion |
| nausea/vomiting | sweating | rash |

Tell your healthcare provider about any side effects that bother you or do not go away. These are not all the possible side effects with ADVATE. You can ask your healthcare provider for information that is written for healthcare professionals.

### What else should I know about ADVATE and Hemophilia A?

Your body may form inhibitors to factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop ADVATE 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.

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

**The risk information provided here is not comprehensive. To learn more, talk with your health care provider or pharmacist about ADVATE. The FDA approved product labeling can be found at www.ADVATE.com or 1-877-825-3327. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.**

Patented: see https://www.shire.com/legal-notice/product-patents
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**REFERENCES: 1.** ADVATE Prescribing Information. **2.** Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management [published correction appears in *J Thromb Haemost.* 2012;10(6):1204]. *J Thromb Haemost.* 2012;10(3):359-367. **3.** Shapiro AD, Schoenig-Diesing C, Silvati-Fidell L, Wong WY, Romanov V. Integrated analysis of safety data from 12 clinical interventional studies of plasma- and albumin-free recombinant factor VIII (rAHF-PFM) in haemophilia A. *Haemophilia.* 2015;21(6):791-798. **4.** Auerswald G, Thompson AA, Recht M, et al. Experience of Advate rAHF-PFM in previously untreated patients and minimally treated patients with haemophilia A. *Thromb Haemost.* 2012;107(6):1072-1082. **5.** myPKFiT for Healthcare Professionals v3.0 User Manual. 2018. **6.** Grillberger L, Kreil TR, Nasr S, Reiter M. Emerging trends in plasma-free manufacturing of recombinant protein therapeutics expressed in mammalian cells. *BiotecSol J.* 2009;4(2):186-201. **7.** Takeda data on file.



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