Winter 2014/2015

KHF Hemosphere

# One Tough Mudder

*"It's a great excuse to be a kid again and go play in the mud." ~ Daniel Cieslak*

Daniel and Amanda after their 2014 Tough Mudder

Daniel Cieslak has severe hemophilia A (factor 8 deficiency), yet that doesn't keep him down. Quite the opposite in fact—because for the past 2 years, Daniel has participated in an event called Tough Mudder. Tough Mudder is a nation-wide, team-oriented 10-12 mile obstacle course designed to test a person's physical strength and mental grit.

Daniel stongly believes in having an active lifestyle, "*…one thing I saw at Camp Discovery—kids would not be getting enough exercise in their daily lives so their joints weren't as healthy as they could have been and that caused problems for the kids.*"

Daniel said he learned about the event through his friends. "*I did it because I wanted to prove to myself that I could complete one.*" He finished his first Tough Mudder in November of 2013 and his second last May along with his girlfriend Amanda. "*You will be dead-tired afterwards, but it feels really good knowing you accomplished something.*"

Daniel really likes the team aspect of the event. "*One great part of the Tough Mudder mantra is the idea that the Mudder is not a race for best time, but a race to work together with others to complete it. In fact many of the obstacles are almost impossible without the help of others. I think it's of the utmost importance for us to step back and remember we are all here running the race of life together, which has a lot of obstacles we can't complete on our own.*"

He has 2 favorite Tough Mudder obstacles. "*The first obstacle is called 'Arctic Enema' and it basically consists of a pool filled with ice and water. The temperature of the water is just above freezing so it's a huge shock to the body.* The second "*…is about ten yards of mud and small hay bales with electrically charged wires hanging down from above. The goal is to run through without getting shocked, but that almost never happens. I loved that one for the adrenaline rush, but it's definitely not something I would do on a regular basis. Call me crazy, but the ones that seem the most extreme usually end up being the most fun.*"

Daniel is seriously considering doing it all again this June at a Tough Mudder event at the Kentucky Speedway in Sparta, KY. He may be crazy, but he sure is tough!

**KHF Spotlight**

# Gene Therapy Study Still Succeeding Three Years Later

It has now been three years since a group of patients with severe hemophilia B, or factor IX (FIX) deficiency, in London received a single dose of gene therapy as part of a new clinical trial. Early results of the trial were positive as these patients began to generate FIX levels ranging from 1%-6%. Prior to the study, they produced little to none of the crucial clotting factor protein.

> I think it's going to have a big impact.
>
> *~Timothy Nichols, MD*

This seemingly modest boost in FIX "expression" is important. The increase in FIX essentially transforms a patient symptomatically, from severe to mild, with the end result a significant, even dramatic, reduction in bleeds. Results described in a new article indicate that the initial breakthrough results have been sustained during the three years since the study began in 2011.

The report, "Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B," was published in the November 20, 2014, issue of The New England Journal of Medicine. The lead author of the update was Andrew Davidoff, MD, St. Jude Children's Research Hospital in Memphis, TN. Davidoff has collaborated for more than a decade with a strong team of researchers, including coauthor Amit Nathwani, MD, PhD, at the University College London. "I believe that, scientifically, this is ready for prime time," said Davidoff.

The gene therapy trial employed an adeno-associated virus serotype 8 (AAV8), a small virus that does not cause disease and produces mild immune responses, as a vector (delivery vehicles) to introduce a functioning FIX gene into the liver cells of subjects with severe hemophilia B. The goal of the trial was to trigger viable, long-term FIX protein production through a single administration of the therapy.

Overall, 10 subjects with severe hemophilia B participated in the study, six of whom received high doses of AAV8 and reached average FIX levels of 5.1%. According to investigators, this "resulted in a reduction of more than 90% in both bleeding episodes and the use of prophylactic factor IX concentrate." Also, no toxic effects were reported.

"I think it's going to have a big impact. The study showed both safety and efficacy, and the side effects were minimal," said Timothy Nichols, MD, who heads the Francis Owen Blood Research Laboratory at the University of North Carolina at Chapel Hill. He was not involved in the study. "This is a single shot of medicine given to patients who are treating themselves two or three times a week," he told Reuters Health over the phone. "Suddenly, they don't have to take the medicine anymore."

*Source: Reuters, November 19, 2014*

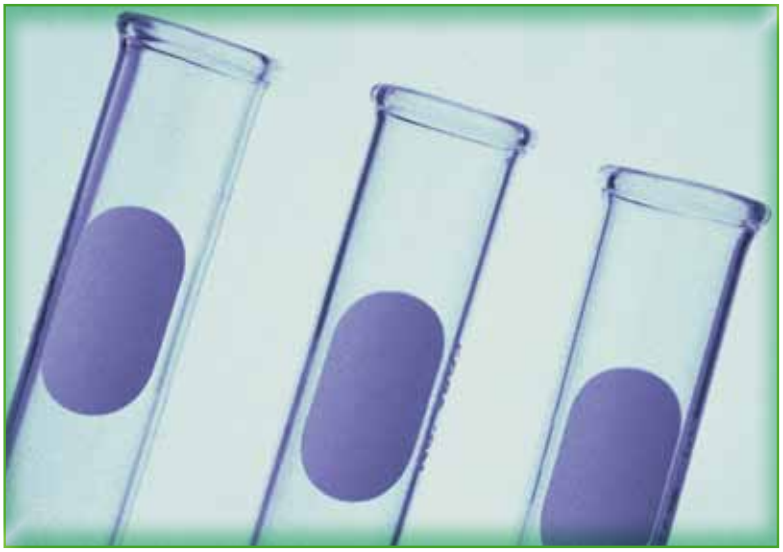
# Plant-Based Inhibitor Therapy Continues to Evolve

Scientists from the University of Florida in Gainesville (UF-G) and the University of Pennsylvania (U-Penn) continue to investigate an experimental, plant cell-based approach to preventing inhibitors and allergic reactions (anaphylaxis) to clotting factor therapies in people with hemophilia. An update on their progress was published online, December 16, 2014, in Scientific American, a division of Nature America, Inc.

Lead investigator Henry Daniell, PhD, director of translational research at the U-Penn School of Dental Medicine, and Roland W. Herzog, PhD, a molecular biologist at UF-G, have, for several years, been working on a technique that involves encapsulating an orally administered "tolerance-inducing protein" such as factor IX (FIX) within plant cell walls. When ingested, the bio-encapsulated protein safely travels through the stomach before reaching the small intestines. The plant cell wall shields the FIX from being prematurely broken down by stomach acid. Eventually, microorganisms eat away the cell wall, gradually releasing the protein.

Building on earlier studies (2010) that successfully used bioengineered tobacco plant cells to prevent inhibitors and anaphylaxis in mice with hemophilia B (FIX deficiency), Daniell and Herzog are now turning to freeze-dried lettuce leaf cells engineered to trigger a high concentration of FIX. Each lettuce leaf cell contains approximately 10,000 chloroplasts, each structured in such a way to hold very large volumes of the FIX protein. Chloroplasts are subunits of plant cells, most often known as crucial components of photosynthesis. Although these chloroplast-rich plant cells are not equipped to prevent bleeding—plants are unable to make human clotting factors biologically active—they have shown an ability to induce tolerance in the immune system to FIX. Researchers have been developing this novel therapeutic approach for several years to create potential vaccines against malaria and cholera, and genetically engineered insulin to help prevent diabetes.

Daniell and Herzog recently took the next step and tested this approach in two dogs with hemophilia B. They fed both dogs their normal food along with the engineered lettuce cells converted into a green powder form. There have been no reports of anaphylaxis or inhibitors in the mice from the earlier study or in the dogs that recently received the plant-based therapy. "So far, it's going very well," reported Daniell. If this novel oral therapy continues to prevent treatment complications in animal models, the next step will be to replicate that success in human clinical studies.



Source: *Scientific American*, December 16, 2014

# **Event** News

## KHF's Holiday Event Rounded Out the Year With High Spirits

A record number of guests enjoyed the fellowship, festive ambience, and all the trimmings of this year's KHF holiday event at the Highland Legion Post in Louisville. Santa brought gifts for every child in attendance, which resulted in more than sixty smiles and happy faces. Holiday crafts and a Christmas play were presented Christian Fellowship's youth group under the leadership of the talented Connie Thacker. Adults had a chance to choose from an attractive selection of door prizes and bid on must-have items in the silent auction. Young and young at heart alike enjoyed the delectable array of hors d'oeuvres prepared by Chef John Taylor followed by sweet samplings of bake contest entries.

Congratulations to Nicki Lennon for winning the bake contest with a delightful and sumptuous Mocha Truffle Cheesecake, followed by Leslie Houvenagle with her tasty Weight Watchers Pecan Pie, and David Houvenagle with a his yummy Mint Chocolate Cheesecake. Guests also mingled with our year-end event sponsors who were **Accredo, Amerimed, Baxter BioScience, Bayer HealthCare, Biogen Idec, CSL Behring, CVS Caremark, Grifols, Matrix Health, Novo Nordisk, Octapharma, and Walgreens Infusion Services**, and ***special thanks to Jack and Susan Leffew for their generous donation.***

## Kentucky Hemophilia Advocacy Day

KHF's second annual Advocacy Day in Frankfort was another resounding success. Advocates from Kentucky's bleeding disorders community travelled to Frankfort on February 11, 2015 to call on their legislators. After a brief, early morning orientation and introduction to the day's activities, participants had the opportunity to meet with their legislators and 1) educate them about bleeding disorders and related issues, 2) thank them for continued funding of the existing patient assistance program available through the Commission for Children with Special Health Care Needs, and 3) seek their support for the Cap the Copay Campaign.

The goal of the Cap the Copay Campaign is to limit the copay amounts that currently are being charged for specialty drugs, such as factor products and other expensive medications needed for patients with

## Kentucky Hemophilia Advocacy Day cont…

chronic but treatable conditions, that allow them to function and have a decent quality of life. Senate Bill 31 and House Bill 146 delineate the details of the proposed legislation that would achieve this cap and make high cost specialty drugs affordable for people who need them to live. Cap Copay advocates were hoping that these bills would come to a vote in this legislative session.

After the morning's excitement and many visits with interested and concerned legislators, this year's advocacy day ended with a wrap-up luncheon at Serafini Restaurant in downtown Frankfort.

Sponsors of this important event were **Accredo, Baxter BioScience, Biogen Idec, CSL Behring, Novo Nordisk, and Pfizer**. Advocacy Day was a joint activity with the **Tri-State Bleeding Disorder Foundation**, which also serves several counties in northern Kentucky.

We thank **Kelly Fitzgerald and Mark Hobraczk from PSI, Lisa Raterman, Kim Jones, Melissa Bowie, and Mike Vogel** for helping us plan and organize this important event.

# Washington Days

Washington Days is the National Hemophilia Foundation's annual advocacy activity in Washington, DC. Reportedly, a record number of 300 attendees from 45 states and Puerto Rico representing the bleeding disorders community, participated in this national advocacy event on February 25-27, 2015.


This year, advocates asked Congress to 1) support maintaining funding for the federal hemophilia programs at the Maternal and Child Health Bureau (MCHB) and Centers for Disease Control and Prevention (CDC) in their appropriations requests; 2) co-sponsor Representative Aaron Schock's (IL-18) legislation to improve access to skilled nursing facilities (SNFs) for hemophilia patients in the House or introduce companion legislation in the Senate; and 3) co-sponsor the Patients' Access to Treatment Act (House) or introduce companion legislation (Senate) to increase access to life-saving drugs on specialty tiers by prohibiting insurers from imposing exorbitant co-insurance requirements on patients.

Representing KHF were **Eric and Venus Marcum** from Louisville. Venus serves on KHF's Board of Directors and Eric served previously as a KHF board member and president of the board.

# More News

## Upcoming
# KHF Events

Don't forget to mark your calendars for all of these fun events! Plus, remember our fund raisers help raise money for services for those in our community with bleeding disorders. Please help in any way you can.

# 2014–2015 Kentucky Hemophilia Foundation Membership

***We thank these members of the Kentucky Hemophilia Foundation for their support!***

**Individual/Family Memberships, 20+**
Susan Geralds
Frances Joyce Lewis

**Supporting Memberships, $35+**
Judy Hayes
in memory of Michael Jason Hayes
Barbara Hendrix
Glen & Deborah Hitt
Mike Marlier
Don Mattingly
John & Carol Nord

**Patron Memberships, $50+**
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David & Leslie Houvenagle
Laura & Glen Webb

**Sustaining Memberships, $100+**
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Barbara Grayson
Charles & Ruth Hall
Fred & Darline Hartman
Thomas & Alice Hendrix
Venus & Eric Marcum
Keith Peterson
Kim Wearsch

**Benefactor Memberships, $250+**
Mark Osborne
Bill Stopher

**Champion/Corporate Memberships, $500+**
Ted & Jennifer Forcht
Terry & Marion Forcht

# In Memory

## September 1, 2014 — November 30, 2014

*Gone from our sight but never our memories; gone from our touch but never our hearts…*

Jeremy D. Clary
Pat & Lisa Mattingly

William L. Farmer, Sr.
Mrs. William L. Farmer, Sr.

William L. Farmer, Sr.
Mrs. William L. Farmer, Sr.

Reverend Daniel L. Goff
Pat & Lisa Mattingly

Spalding Grayson
at Christmas
Frances Joyce Lewis

Alan Taylor Hall
Mr. & Mrs. Walter Hall

# Do The Five

***Follow these steps to prevent or reduce complications of bleeding disorders***

1. Get an annual comprehensive checkup at a hemophilia treatment center.
2. Get vaccinated – Hepatitis A and B are preventable.
3. Treat bleeds early and adequately.
4. Exercise to protect your joints.
5. Get tested regularly for blood-borne infections.

To find out more about the National Prevention Program developed by the National Hemophilia Foundation in collaboration with the Centers for Disease Control and Prevention (CDC), click on www.hemophilia.org or call toll-free 800-42-HANDI.

**Stay connected with KHF**
**kyhemo.org**

*KHF neither recommends nor endorses the products in this publication and does not make recommendations concerning treatment regimen for individuals. KHF suggests that you consult your physician or treatment center before pursuing any course of treatment. This publication is for general information only.*

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ADVATE
[Antihemophilic Factor (Recombinant)]
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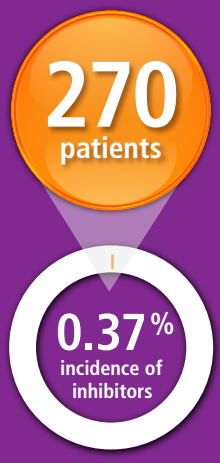


Low PTP inhibitor rate[1-5]
(95% confidence interval, 0.02%-2.13%)

## ADVATE HAS A PROVEN SAFETY PROFILE[1-7]

### LOW RISK OF INHIBITOR DEVELOPMENT DEMONSTRATED IN CLINICAL STUDIES

Six clinical studies of 270 previously treated patients (PTPs) with moderately severe to severe hemophilia A demonstrated a low inhibitor rate of 0.37%.[1-5] PTPs are considered to be the most appropriate study population for the assessment of product-related immunogenicity.[8]

# INDICATIONS

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] 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 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.

# DETAILED IMPORTANT RISK INFORMATION

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.

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.
- Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

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.

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, and rash.

Tell your healthcare provider 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.**

**Please see Brief Summary of ADVATE Prescribing Information on the following page.**

**References: 1.** 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. *J Thromb Haemost*. 2012;10(3):359-367. **2.** Shapiro A, Gruppo R, Pabinger I, et al. Integrated analysis of safety and efficacy of a plasma- and albumin-free recombinant factor VIII (rAHF-PFM) from six clinical studies in patients with hemophilia A. *Expert Opin Biol Ther*. 2009;9(3):273-283. **3.** Tarantino MD, Collins PW, Hay CRM, et al, and the rAHF-PFM Clinical Study Group. Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia*. 2004;10(5):428-437. **4.** Négrier C, Shapiro A, Berntorp E, et al. Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of Advate in previously treated patients. *Thromb Haemost*. 2008;100(8):217-223. **5.** Blanchette VS, Shapiro AD, Liesner RJ, et al, for the rAHF-PFM Clinical Study Group. Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients. *J Thromb Haemost*. 2008;6(8):1319-1326. **6.** Oldenburg J, Goudemand J, Valentino L, et al. Postauthorization safety surveillance of ADVATE [antihemophilic factor (recombinant), plasma/albumin-free method] demonstrates efficacy, safety and low-risk for immunogenicity in routine clinical practice. *Haemophilia*. 2010;16(6):866-877. **7.** 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. **8.** White GC, DiMichele D, Mertens K, et al. Utilization of previously treated patients (PTPs), noninfected patients (NIPs), and previously untreated patients (PUPs) in the evaluation of new factor VIII and factor IX concentrates. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*. 1999;81(3):462.



Baxter

**ADVATE [Antihemophilic Factor (Recombinant)]**
**Lyophilized Powder for Reconstitution for Intravenous Injection**
**Brief Summary of Prescribing Information: Please see package insert for full Prescribing Information.**

## INDICATIONS AND USAGE

ADVATE [Antihemophilic Factor (Recombinant)] is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for:

- Control and prevention of bleeding episodes.
- Perioperative management.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ADVATE is not indicated for the treatment of von Willebrand disease.

## CONTRAINDICATIONS

ADVATE is contraindicated in patients who have life-threatening hypersensitivity reactions, including anaphylaxis, to mouse or hamster protein or other constituents of the product (mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and/or glutathione).

## WARNINGS AND PRECAUTIONS

### Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. Symptoms include dizziness, paresthesia, rash, flushing, facial swelling, urticaria, dyspnea, and pruritus.

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG) ≤0.1 ng/IU ADVATE, and hamster proteins ≤1.5 ng/IU ADVATE. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Discontinue ADVATE if hypersensitivity symptoms occur and administer appropriate emergency treatment.

### Neutralizing Antibodies

Neutralizing antibodies (inhibitors) have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs). Monitor all patients for the development of factor VIII inhibitors by appropriate clinical observation and laboratory testing. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures factor VIII inhibitor concentration. [see *Warnings and Precautions*]

### Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained when clinically indicated. [see *Dosage and Administration*]
- Perform the Bethesda assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of ADVATE, use Bethesda Units (BU) to titer inhibitors.
  - If the inhibitor titer is less than 10 BU per mL, the administration of additional antihemophilic factor concentrate may neutralize the inhibitor and may permit an appropriate hemostatic response.
  - If the inhibitor titer is above 10 BU per mL, adequate hemostasis may not be achieved. The inhibitor titer may rise following ADVATE infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

## ADVERSE REACTIONS

The serious adverse reactions seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.

The most common adverse reactions observed in clinical trials (frequency ≥10% of subjects) were pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury.

### Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

ADVATE has been evaluated in five completed clinical trials in previously treated patients (PTPs) and one ongoing trial in previously untreated patients (PUPs) with severe to moderately severe hemophilia A (factor VIII ≤2% of normal). A total of 234 subjects have been treated with ADVATE as of March 2006. Total exposure to ADVATE was 44,926 infusions. The median duration of participation per subject was 370.5 (range: 1 to 1,256) days and the median number of exposure days to ADVATE per subject was 128 (range: 1 to 598).[3]

The summary of adverse reactions with a frequency ≥5% (defined as adverse events occurring within 24 hours of infusion or any adverse event causally related occurring within the trial period) is shown in Table 3.

No subject was withdrawn from a clinical trial due to an adverse reaction. There were no deaths in any of the clinical trials.

**Table 3**
**Summary of Adverse Reactions[a] with a Frequency ≥5% (N = 234 Treated Subjects[b])**

| MedDRA[c] System Organ Class | MedDRA Preferred Term | Number of ADRs | Number of Subjects | Percent of Subjects |
|---|---|---|---|---|
| General disorders and administration site conditions | Pyrexia | 78 | 50 | 21 |
| Nervous system disorders | Headache | 104 | 49 | 21 |
| Respiratory, thoracic, and mediastinal disorders | Cough | 75 | 44 | 19 |
| Infections and infestations | Nasopharyngitis | 61 | 40 | 17 |
| Gastrointestinal disorders | Vomiting | 35 | 27 | 12 |
| Musculoskeletal and connective tissue disorders | Arthralgia | 44 | 27 | 12 |
| Injury, poisoning, and procedural complications | Limb injury | 55 | 24 | 10 |
| Infections and infestations | Upper respiratory tract infection | 24 | 20 | 9 |
| Respiratory, thoracic, and mediastinal disorders | Pharyngolaryngeal pain | 23 | 20 | 9 |
| Respiratory, thoracic, and mediastinal disorders | Nasal congestion | 24 | 19 | 8 |
| Gastrointestinal disorders | Diarrhea | 24 | 18 | 8 |
| Gastrointestinal disorders | Nausea | 21 | 17 | 8 |
| General disorders and administration site conditions | Pain | 19 | 17 | 8 |
| Skin and subcutaneous tissue disorders | Rash | 16 | 13 | 6 |
| Infections and infestations | Ear infection | 16 | 12 | 5 |
| Injury, poisoning, and procedural complications | Procedural pain | 16 | 12 | 5 |
| Respiratory, thoracic, and mediastinal disorders | Rhinorrhea | 15 | 12 | 5 |

[a] Adverse reactions are defined as all adverse events that occurred (a) within 24 hours after being infused with investigational product, or (b) all adverse events assessed related or possibly related to investigational product, or (c) adverse events for which the investigator's or sponsor's opinion of causality was missing or indeterminate.

[b] The ADVATE clinical program included 234 treated subjects from 5 completed studies in PTPs and 1 ongoing trial in PUPs as of 27 March 2006.

[c] MedDRA version 8.1 was used.

*Immunogenicity*

The development of factor VIII inhibitors with the use of ADVATE was evaluated in clinical trials with pediatric PTPs (<6 years of age with >50 factor VIII exposures) and PTPs (>10 years of age with >150 factor VIII exposures). Of 198 subjects who were treated for at least 10 exposure days or on study for a minimum of 120 days, 1 adult developed a low-titer inhibitor (2 BU in the Bethesda assay) after 26 exposure days. Eight weeks later, the inhibitor was no longer detectable, and *in vivo* recovery was normal at 1 and 3 hours after infusion of another marketed recombinant factor VIII concentrate. This single event results in a factor VIII inhibitor frequency in PTPs of 0.51% (95% CI of 0.03 and 2.91% for the risk of any factor VIII inhibitor development).[3,4] No factor VIII inhibitors were detected in the 53 treated pediatric PTPs.

In clinical trials that enrolled previously untreated subjects (defined as having had up to 3 exposures to a factor VIII product at the time of enrollment) , 5 (20%) of 25 subjects who received ADVATE developed inhibitors to factor VIII.[3] Four subjects developed high titer (>5 BU) and one patient developed low-titer inhibitors. Inhibitors were detected at a median of 11 exposure days (range 7 to 13 exposure days) to investigational product.

Immunogenicity also was evaluated by measuring the development of antibodies to heterologous proteins. 182 treated subjects were assessed for anti-Chinese hamster ovary (CHO) cell protein antibodies. Of these subjects, 3 showed an upward trend in antibody titer over time and 4 showed repeated but transient elevations of antibodies. 182 treated subjects were assessed for mulgG protein antibodies. Of these, 10 showed an upward trend in anti-mulgG antibody titer over time and 2 showed repeated but transient elevations of antibodies. Four subjects who demonstrated antibody elevations reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts. All of these subjects had numerous repeat exposures to the study product without recurrence of the events and a causal relationship between the antibody findings and these clinical events has not been established.

Of the 181 subjects who were treated and assessed for the presence of anti-human von Willebrand Factor (VWF) antibodies, none displayed laboratory evidence indicative of a positive serologic response.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADVATE with the incidence of antibodies to other products may be misleading.

### Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ADVATE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with ADVATE, cases of serious allergic/hypersensitivity reactions including anaphylaxis have been reported and factor VIII inhibitor formation (observed predominantly in PUPs). Table 4 represents the most frequently reported post-marketing adverse reactions as MedDRA Preferred Terms.

**Table 4**
**Post-Marketing Experience**

| Organ System [MedDRA Primary SOC] | Preferred Term |
|---|---|
| Immune system disorders | Anaphylactic reaction[a]<br>Hypersensitivity[a] |
| Blood and lymphatic system disorders | Factor VIII inhibition |
| General disorders and administration site conditions | Injection site reaction<br>Chills<br>Fatigue/Malaise<br>Chest discomfort/pain<br>Less-than-expected therapeutic effect |

[a] These reactions have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and/or pruritus.



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**This information is not intended to replace discussions with your healthcare provider.**

## Indications

ELOCTATE [Antihemophilic Factor (Recombinant), Fc Fusion Protein] is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: control and prevention of bleeding episodes, perioperative management (surgical prophylaxis), and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ELOCTATE is not indicated for the treatment of von Willebrand disease.

## Important Safety Information

Do not use ELOCTATE if you have had an allergic reaction to it in the past.

Tell your healthcare provider if you have or have had any medical problems, take any medicines, including prescription and non-prescription medicines, supplements, or herbal medicines, have any allergies, are breastfeeding, are pregnant or planning to become pregnant, or have been told you have inhibitors (antibodies) to Factor VIII.

Allergic reactions may occur with ELOCTATE. Call your healthcare provider or get emergency treatment right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash, or hives.

Your body can also make antibodies called, "inhibitors," against ELOCTATE, which may stop ELOCTATE from working properly.

Common side effects of ELOCTATE are joint pain and general discomfort. These are not all the possible side effects of ELOCTATE. Talk to your healthcare provider right away about any side effect that bothers you or that does not go away, and if bleeding is not controlled after using ELOCTATE.

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.

**Please see Brief Summary of full Prescribing Information on the next page.**

biogen idec®

**FDA-Approved Patient Labeling**

**Patient Information**

**ELOCTATE™ /el' ok' tate/**
**[Antihemophilic Factor (Recombinant), Fc Fusion Protein]**

Please read this Patient Information carefully before using ELOCTATE and each time you get a refill, as there may be new information. This Patient Information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is ELOCTATE?**
ELOCTATE is an injectable medicine that is used to help control and prevent bleeding in people with Hemophilia A (congenital Factor VIII deficiency).

Your healthcare provider may give you ELOCTATE when you have surgery.

**Who should not use ELOCTATE?**
You should not use ELOCTATE if you had an allergic reaction to it in the past.

**What should I tell my healthcare provider before using ELOCTATE?**
Talk to your healthcare provider about:

- Any medical problems that you have or had.
- All prescription and non-prescription medicines that you take, including over-the-counter medicines, supplements or herbal medicines.
- Pregnancy or if you are planning to become pregnant. It is not known if ELOCTATE may harm your unborn baby.
- Breastfeeding. It is not known if ELOCTATE passes into the milk and if it can harm your baby.

**How should I use ELOCTATE?**
You get ELOCTATE as an infusion into your vein. Your healthcare provider will instruct you on how to do infusions on your own, and may watch you give yourself the first dose of ELOCTATE.

Contact your healthcare provider right away if bleeding is not controlled after using ELOCTATE.

**What are the possible side effects of ELOCTATE?**
Common side effects of ELOCTATE are joint pain and general discomfort.

Allergic reactions may occur. Call your healthcare provider or emergency department right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash or hives.

Your body can also make antibodies called, "inhibitors," against ELOCTATE, which may stop ELOCTATE from working properly. Your healthcare provider may give you blood tests to check for inhibitors.

**How should I store ELOCTATE?**

- Keep ELOCTATE in its original package.
- Protect it from light.
- Do not freeze.
- Store refrigerated (2°C to 8°C or 36°F to 46°F) or at room temperature [not to exceed 30°C (86°F)], for up to six months.
- When storing at room temperature:
  - Note on the carton the date on which the product is removed from refrigeration.
  - Use the product before the end of this 6 month period or discard it.
  - Do not return the product to the refrigerator.

Do not use ELOCTATE after the expiration date printed on the vial or, if you removed it from the refrigerator, after the date that was noted on the carton, whichever is earlier.

After reconstitution (mixing with the diluent):

- Do not use ELOCTATE if the reconstituted solution is not clear to slightly opalescent and colorless.
- Use reconstituted product as soon as possible
- You may store reconstituted solution at room temperature, not to exceed 30°C (86°F), for up to three hours. Protect the reconstituted product from direct sunlight. Discard any product not used within three hours.

**What else should I know about ELOCTATE?**
Medicines are sometimes prescribed for purposes other than those listed here. Do not use ELOCTATE for a condition for which it was not prescribed. Do not share ELOCTATE with other people, even if they have the same symptoms that you have.

Manufactured by:
Biogen Idec Inc.
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