Spring/Summer 2015

KHF Hemosphere

Vegasville was a Blast!

Our 2015 Vegasville Gala fundraiser at the Olmsted in Louisville was enjoyed by all who attended and raised essential funds for KHF's programs and services. Steve Fazzini from Toledo, Ohio, entertained during the cocktail hour and dinner with a medley of Vegas hits and Italian classics. After dinner, dance music was provided by the band Indigo, a Louisville favorite on the music scene. Our gaming tables attracted quite a crowd, and the west wing was all abuzz when it came time for the grand prize drawing.

The grand prize package consisting of a 14 kt. white gold London topaz necklace, weekend use of a BMW convertible, hotel accommodations, and dinner gift certificate was won by Rania Salem from Matrix Health. Thanks to a generous donation by Kosair Charities, the Special Ask Auction during dinner raised $10,000. We thank all table sponsors, contributors, and in-kind donors for helping us raise a total of $58,000.

Sponsors were Forcht Bancorp, Baxalta (formerly Baxter), Kosair Charities, Bayer HealthCare, Biogen (formerly Biogen Idec), CSL Behring, CVS Caremark, Matrix Health, Novo Nordisk, Option Care (formerly Walgreens Infusion Services), Pfizer, Express Scripts dba Accredo, Mr. & Mrs. Henry W. Boyd, III, Louisville Oral Surgery & Dental Implants, and Republic Bank and Trust Company. Major in-kind donors were Business First, Louisville Oral Surgery & Dental Implants, Publishers Printing, Sam Swope BMW, Val's Gems and Repair, and Welch Printing. Special thanks to our gaming volunteers, John Silletto and friends; our MC, Ben Pine, Chief Meteorologist at WHAS 11; and the Hitt family for facilitating the Special Ask.

Gene Therapy Study in Dogs Shows Markedly Lower Bleeding Rates

In a recently published paper, an international team of researchers report effectively administering gene therapy to three dogs with hemophilia B in an ongoing study. The report, "Liver-Directed Lentiviral Gene Therapy in a Dog Model of Hemophilia B," was published March 4, 2015, in the journal Science Translational Medicine. The lead author of the paper was Luigi Naldini, MD, PhD, director of the San Raffaele Telethon Institute for Gene Therapy at the San Raffaele Scientific Institute in Milan, Italy.

The three dogs in the study were administered the gene therapy either through direct injection into the liver, a primary source of clotting factor protein production, or intravenously. The therapy was housed in repurposed retroviruses called lentiviral vectors. These vectors act as vehicles, carrying customized genetic material to elicit the production of factor IX (FIX). One advantage in using lentiviruses is that a majority of patients do not generate antibodies to this type of vector, avoiding an immune response that would otherwise render the treatment ineffective. Another benefit of using lentiviral vectors is their large size, enabling them to deliver greater concentrations of the FIX gene, resulting in a more optimal therapeutic effect.

Three years after administering the treatment, Naldini and his colleagues report significant symptomatic improvement. Prior to receiving the therapy, the dogs experienced approximately five spontaneous bleeds per year. In contrast, in the three years since receiving therapy, the dogs have averaged 0 to 1 bleed per year. This notable decrease in spontaneous bleeding events was achieved because the gene therapy boosted FIX generation in the dogs from virtually 0 to 1%-3%. This seemingly modest increase was enough to dramatically lower bleeding rates.

"The result was stunning," said Timothy Nichols, MD, director of the Francis Owen Blood Research Laboratory at the University of North Carolina School of Medicine and co-senior author of the paper. "Just a small amount of new factor IX necessary for proper clotting produced a major reduction in bleeding events. It was extraordinarily powerful."

Investigators have also reported no harmful side effects. Safety being a primary concern, Naldini and his team performed additional studies in types of mice that are more likely to develop complications from lentiviruses, such as malignancies. No hazardous responses to the therapy were reported. "Considering the mouse model data and the absence of detectable genotoxicity during long-term expression in the hemophilia B dogs, the lentiviral vectors have a very encouraging safety profile in this case," said Nichols.

Ideally, Naldini, Nichols and their team would like to increase FIX production to 5%-10% to essentially eradicate spontaneous bleeding in patients with hemophilia B. To reach this endpoint, several years of additional investigation, including larger animal studies and eventual human clinical trials, will need to occur.

Source: ScienceDaily, March 12, 2015

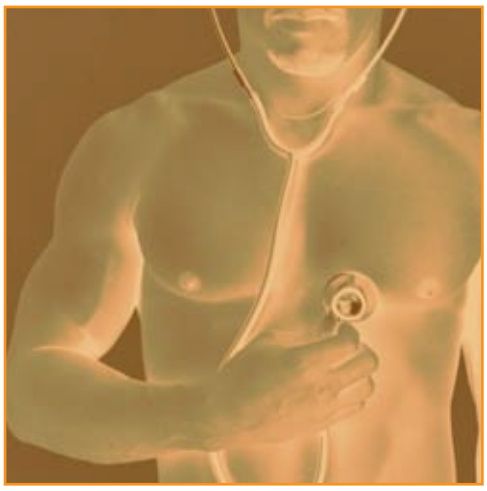
Study Focuses on Cardiovascular Disease in Hemophilia Patients

As life expectancy in people with hemophilia (PWH) continues to rise closer to the national average, hemophilia healthcare providers have grown increasingly interested in the conditions most commonly linked to aging. One of the more pervasive of these is cardiovascular disease (CVD), and associated conditions such as ischemic heart disease (hardening of arteries) and atrial fibrillation (irregular heartbeat rate/rhythm). A multidisciplinary team of investigators conducted a scan and review of medical literature associated with CVD in PWH published between 1980-2013. Their findings, "Consensus Review of the Treatment of Cardiovascular Disease in People with Hemophilia A and B," were published in the March/April issue of the journal Cardiology in Review.

The lead author of the review was Victor Ferraris, MD, PhD, Tyler Gill Professor of Surgery, Division of Cardiovascular and Thoracic Surgery at the University of Kentucky in Lexington. Ferraris and his coauthors acknowledged that data relevant to CVD in PWH is limited. That's because of the low numbers of hemophilia patients who have been documented with complications related to heart disease. The result is a lack of evidence-based guidelines from which to base treatment decisions.

"Accordingly, current recommendations for the medical and surgical management of common cardiovascular conditions in PWH derive from anecdotal experience and expert opinion. Most recommendations reflect guidelines and common practices for people without hemophilia," said Ferraris. "Ultimately, the rigorous, systematic investigation of management strategies for many cardiovascular conditions is unobtainable, given the relative rarity of hemophilia and even smaller numbers of PWH with any given cardiovascular condition."

However, Ferraris and colleagues did arrive at some conclusions. An examination of the literature suggested that low levels of factor VIII or IX did not necessarily offer hemophilia A or B patients extra protection against CVD conditions, including ischemic heart disease. In fact, the authors anticipate that older PWH will experience CVD rates comparable to the general population. Investigators added that recommendations relevant to the medical/surgical management of CVD in the aging PWH will be largely comparable to what is recommended for unaffected patients, as long as factor levels remain high enough to ensure adequate control of bleeds. They also acknowledged that the presence of an inhibitor to infused factor VIII or IX will complicate treatment and management in PWH/CVD considerably. The authors concluded that close collaboration between cardiology specialists and the comprehensive care team is crucial for quality clinical management.



"As the population of PWH ages, cardiovascular health care providers will encounter increasing numbers of PWH presenting with typical age related cardiovascular conditions, in addition to other acquired or congenital conditions spanning all ages," reported the authors. "To optimize resource utilization and clinical outcome and to minimize bleeding risk and complications, close consultation with a hematologist, ideally in association with a hemophilia treatment center, is essential."

Source: *Heplive.com*, June 29, 2015

Event News

2015 Spring Semester Scholarship Awards

A $500 scholarship each was awarded to Kevin Loeser, a sophomore at the University of Louisville's College of Business; and Emily Cieslak, a sophomore in biology at the University of South Carolina's Honors College. Kevin received the Herb Schlaughenhoupt, Jr. Memorial Scholarship award and Emily the Betty Meadors Mattingly Memorial Scholarship award. We congratulate them both and wish them much success with their educational pursuits.

Easter Lily and Spring Flowers Sale

We want to thank our volunteers who sold flowers on our behalf during this year's Flowers Sale. Long-time dedicated volunteers, Janet Goff and Sharon McMahan from Owensboro, generated most orders, followed closely by Pat Cooper from the Kentucky Blood Center in Lexington. We greatly appreciate their willingness and commitment to make this fundraiser a success.

Mini-Marathon Team Challenge

On a very rainy Saturday morning in April, several KHF staff and volunteers set out to conquer the Kentucky Derby Festival's Mini-Marathon in downtown Louisville. Lindsay Martin, Board President, Ashley Lennon, and Ursela Kamala walked and ran a portion of the 13.1 miles, while Nicki Lennon had enough grit, endurance, and stamina to run the entire distance. We are so proud of her for this accomplishment on behalf of Kentucky's Bleeding Disorders Community. We thank our sponsors, Baxalta (formerly Baxter), CSL Behring, and Pfizer who supported this event.

Event News

Men's Retreat

The 2015 Men's Retreat was an overnight support activity for men with a bleeding disorder. Hotel accommodations and an outing to Churchill Downs made this retreat especially enjoyable. Educational sessions were held at Cedar Ridge Camp and Retreat Center where the communal cooking of breakfast offered a special bonding opportunity. This program was supported by Baxalta (formerly Baxter), Biogen (formerly Biogen Idec), CSL Behring, Matrix Health, and Novo Nordisk.

Family Day at the Louisville Zoo

This year's Family Day at the Louisville Zoo and 2015 Walk Call-to-Action event was held the last Saturday in May. More than 225 enthusiastic adults and children from all corners of our state attended. Lunch at the Hillside Gazebo was followed by a special animal presentation and carnival games with awesome prizes for the little ones along with the popular drawing for a large selection of great door prizes. A brief shower descended upon us during the drawing but did not dampen anyone's spirits. Everyone who signed up for our Hemophilia Walk in October received an attractive tote bag and participated in a second drawing for three special prizes.

Exhibitors who supported the event were Baxalta (formerly Baxter), Bayer HealthCare, Biogen (formerly Biogen Idec), CSL Behring, Express Scripts dba Accredo, Grifols, Matrix Health, Novo Nordisk, Octapharma, Option Care (formerly Walgreens Infusion Services), and Pfizer.

More News

2014–2015
Kentucky Hemophilia Foundation
Membership

July 1, 2014 - June 30, 2015

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

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

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

Patron Memberships, $50+
Larry G. Bandy, Sr.
Mark Chavez
Arthur & Terri Hackman
David & Leslie Houvenagle
Laura & Glen Webb

Sustaining Memberships, $100+
Sara Ceresa
Leah Graham
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+
Terry & Marion Forcht
Ted & Jennifer Forcht

In Memory

December 1, 2014 — June 30, 2015

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

Margaret Baird
Karie English

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

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

Betty Goodman
Ron Loeser

Spalding Grayson
on Easter
Frances Joyce Lewis

Regina Loeser
Brian H. Jenkins
Janet McKinley
John & Carol Nord
Tony Sauer
Nick Simon
Gail Yates

More News

Upcoming KHF Events

Mark your calendars for all of these fund-raising events! Our fund raisers help raise money for services for those in our community with bleeding disorders. We invite you to participate or help in any way you can.

Kentucky Hemophilia Walk
Saturday, October 10
Wetherby Park, Middletown KY

Walk2 cure hemophilia KHF

Junior fundraisers for the Kentucky Hemophilia Walk!

Jackson and Isabelle Woods of Louisville have been fundraising all summer for this year's Walk with their neighborhood lemonade stand. They are both looking forward to participating in the Walk and are proud to be able to fundraise for it. Attending KHF's Summer Camp was the only and well-deserved break Jackson and Izzi are taking from their summer fundraiser for the Walk. We commend Jackson and Izzi for their initiative and their willingness to fundraise and walk for a cure. **Sign up for the Walk today** and follow their footsteps! Go to **www.hemophilia.org/walk** and **click on the KY icon**.

Poinsettia Sale Fundraiser
November/December

Holiday Family Support Event
Sunday, December 13

Vegasville Gala & Fundraiser
Saturday, March 5

Vegasville
Betting on a Cure

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)]
There's more to life.

ADVATE SUPPORTS YOU BY IMPROVING YOUR PERSONAL INFUSION EXPERIENCE WITH THE BAXJECT III SYSTEM

The reconstitution process with the BAXJECT III system is easier, faster, and designed for you*

- An all-in-one, connected design[1]
- Broad selection of doses, providing opportunities for single-vial options[1]
- One-step activation with fewer steps for **faster** reconstitution—just press, swirl, flip and withdraw*[1,2]
- **Straightforward** pooling process if more than 1 vial is needed—no additional supplies required[1]

1/2 the time

Reconstitute ADVATE in about **half the time***[2]

*As compared with the BAXJECT II needleless transfer device.

Watch the ADVATE with BAXJECT III system reconstitution video and see how it all comes together at **ADVATE.com**

Share your experience using the ADVATE with BAXJECT III system at **www.BAXJECT3Survey.com**

ADVATE [Antihemophilic Factor (Recombinant)] Important Information

Indications

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 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 following page for Brief Summary of ADVATE full Prescribing Information.

References: 1. ADVATE Prescribing Information. Westlake Village, CA: Baxter Healthcare Corporation; April 2014. **2.** Data on file.

Baxalta

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] Hypersensitivity[a]
Blood and lymphatic system disorders	Factor VIII inhibition
General disorders and administration site conditions	Injection site reaction Chills Fatigue/Malaise Chest discomfort/pain Less-than-expected therapeutic effect

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

Baxter Healthcare Corporation, Westlake Village, CA 91362 USA

U.S. License No. 140 Issued 04/2014

Baxter

Alphanate®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Physician
Preferred

ALPHANATE is the **preferred plasma-derived FVIII** product for the treatment of **hemophilia A** among hematologists practicing in HTCs.*

*Results are statistically significant with a 95% confidence interval with a 6.5% margin of error and are based on a blinded national survey of 75 HTC-based Hematologists from a list of federally and non-federally funded HTCs within the US, conducted and validated by a reputable, independent third party, Adivo Associates LLC, on behalf of Grifols USA from October 2014 - January 2015. In order to qualify to complete the survey, Hematologists were rigorously screened according to market research standards having the necessary experience in the relevant treatment segment. Respondents were asked to assume no difference in terms of availability, cost, and reimbursement when indicating their most preferred plasma-derived FVIII brand.

HTC=Hemophilia Treatment Center; pdFVIII=plasma-derived factor VIII

Learn more at **alphanate.com**

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

- Control and prevention of bleeding in patients with hemophilia A
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with ALPHANATE should be discontinued, and emergency treatment should be sought.

Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

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 more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

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Learn how a prolonged half-life may affect your infusion schedule

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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

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, i 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:
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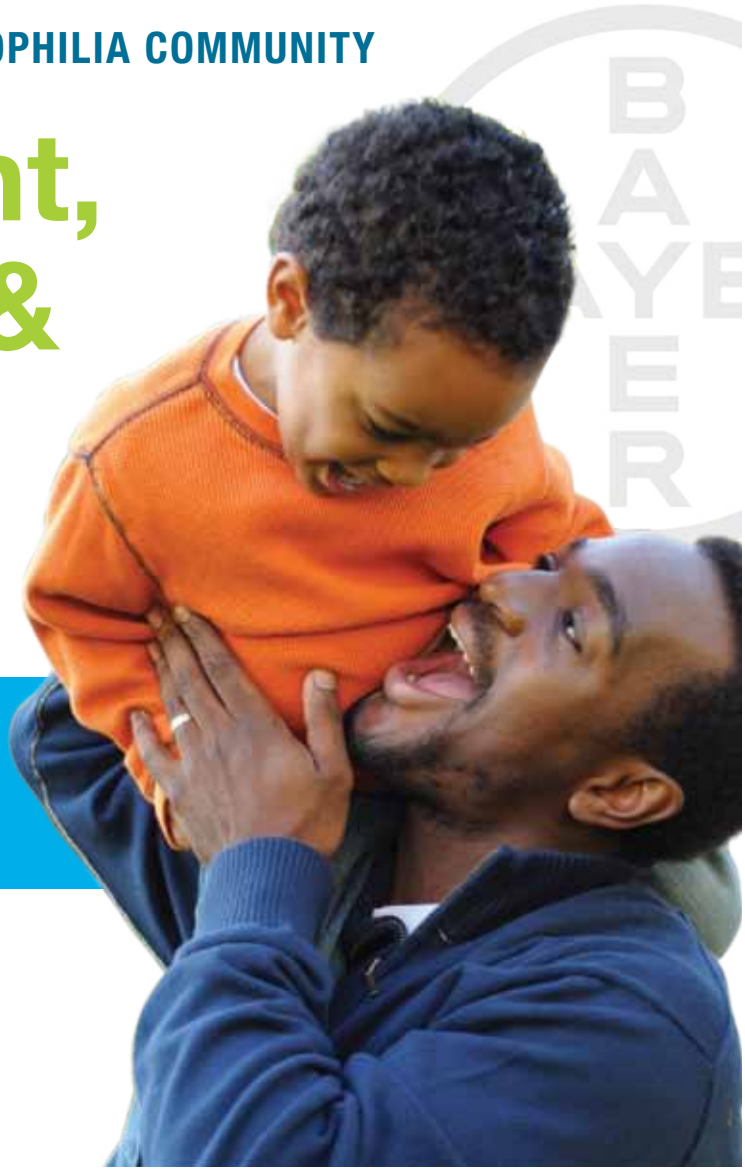
BAYER HEALTHCARE AND THE HEMOPHILIA COMMUNITY

commitment, leadership & innovation



For information on Bayer's Educational Patient and Community Resources, contact your Hematology Account Executive by calling **1-888-79-BAYER**.

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Wetherby Park, Middletown KY

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Simply go to **www.hemophilia.org/walk,** click on the **KY** icon, and follow the prompts.

email: **walk@kyhemo.org**
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800-582-CURE (2873)

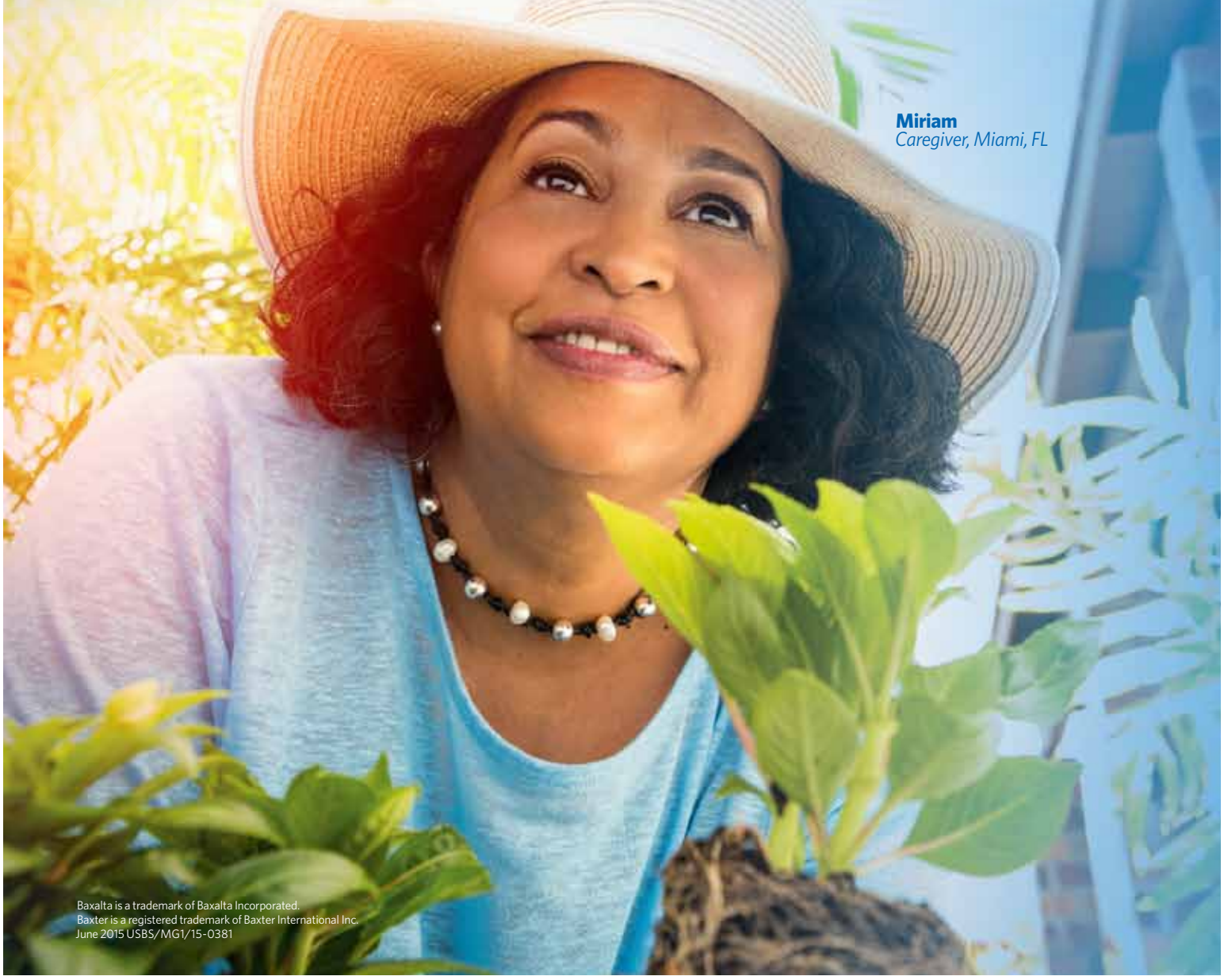
Walk2 cure hemophilia KHF

Our enduring commitment, brighter than ever.

Baxalta

For more than 60 years, we've consistently pursued advancements in the treatment of bleeding conditions.

Now, as Baxter's BioScience becomes Baxalta Incorporated, this proven heritage — along with the advancements we're making today to cultivate tomorrow's developments — fuels our global vision and promise: Our relentless desire to make a meaningful difference in the lives of real people — one person at a time. This promise to you can be seen in all we do, and helps to make us the company we are today.



Miriam
Caregiver, Miami, FL