Fall 2013

KHF Hemosphere

Best camp ever!

"Best camp ever!" This was the compliment heard most frequently at the awards ceremony on Thursday when parents came to pick up their campers after five days and four nights of a continual stream of exciting activities and educational interludes. Twenty-three boys and girls from age seven to seventeen gathered at Cedar Ridge Camp to participate in "Camp Discovery," KHF's annual summer camp program for children and teens with bleeding disorders and their siblings.

Camp activities included a field trip to Skyzone, swimming, canoeing, arts and crafts, team challenge course, Hemophilia Wellness and Infusion class, Capture the Flag game, our version of the Amazing Race, zip lining, and cultural enrichment via Africa Night.

Africa Night featured food samples of Ethiopian Cuisine, a visit by Elizabeth Kizito — Louisville's "Cookie Lady" — who is a native of Uganda and a local entrepreneur. A captivating and informative account of hemophilia care and life in Africa was given by Brandy Trawinski, a nurse from the Indiana Hemophilia Treatment Center, who is part of an outreach team that provides basic hemophilia care in several African counties.

The KHF summer camp is provided free of charge to Kentucky children and teens with bleeding disorders and their siblings. Funding was provided by grants from Kosair Charities and WHAS Crusade for Children and industry contributions by Baxter BioScience, Pfizer, Bayer HealthCare, Novo Nordisk, CSL Behring, Accredo, Grifols, and Kedrion BioPharma.

It's awesome.

I love camp. I have so much fun at camp. Camp Discovery has taught me to self-infuse and so much more about hemophilia. I thank everyone who helps to let me come here. I really enjoy this camp and the people in it. I meet new friends. I look forward to coming to camp. I thank you. I hope to keep coming. All the cooks and counselors take up their time in the summer to let us have fun and eat. I will miss my friends. I had a wonderful time. I want to have fun every year at this camp.
~ KHF Summer 2013 Campers

Grapefruit Juice and Drugs Don't Mix

More than 20 years ago, David G. Bailey, PhD, emeritus professor of physiology, pharmacology, and medicine at the University of Western Ontario, in Canada, discovered that men on felodipine, a calcium channel blocker prescribed to treat high blood pressure, had dangerous amounts of drug in their system after taking it with grapefruit juice. The bioavailability, or amount of drug that reaches the patients' circulation, averaged three times higher than when taken with water.

In 2012, Bailey and co-authors published an updated study of grapefruit-sensitive drugs in the Canadian Medical Association Journal. They identified more than 85 prescription drugs that should not be taken with grapefruit juice. Surprisingly, the amount of grapefruit juice causing problematic reactions was only 200-250 milliliters – 6.76 to 8.45 ounces – when taken with the medication in as few as three days in a row. The grapefruit juice-reacting drugs include antibiotics, cholesterol-lowering drugs called statins, and common pain relievers. Grapefruit, Seville oranges, tangelos, and pomelos all contain furanocoumarin, the chemical that causes the drug interaction.

The adverse effects from grapefruit juice depend on the medication taken. They can include dizziness, drowsiness, and gastrointestinal bleeding. One severe reaction called rhabdomyolysis, or muscle breakdown, causes muscle fibers called myglobin to be released into the bloodstream, eventually impairing kidney cells. Other severe side effects include liver damage, respiratory depression, and torsade de pointes, an elevated heartbeat caused by rapid contraction of the ventricles. Torsade de pointes is a life-threatening arrhythmia that can be fatal. Consult your pharmacist about your prescription drugs and possible interactions.

Learn More: Bailey DG, et al. Interaction of citrus juices with felodipine and nifedipine. Lancet 1991; 337 (8736): 268-9; Bailey DG, et al. Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? Canadian Medical Association Journal 2012; DOI: 10.1503/cmaj.120951.

Excerpt of article by Sarah Aldridge, Hemaware, Summer 2013, Vol. 18, Issue 3.

Experimental bleeding disorder therapy under way

FDA Grants Orphan Drug Status to Alnylam's Hemophilia Therapy

In August, Alnylam Pharmaceuticals, Inc., announced that the US Food and Drug Administration (FDA) had granted Orphan Drug Designation to ALN-AT3 for the treatment of hemophilia A. The company, based in Cambridge, Massachusetts, is developing ALN-AT3, a subcutaneously administered (injection just under the skin) RNAi therapy that targets antithrombin (AT) as a way to treat hemophilia A or B, hemophilia A or B with inhibitors, and other rare bleeding disorders. AT is a small plasma protein molecule that inactivates factor Xa and thrombin, which are needed for blood clotting.

ALN-AT3 incorporates Alnylam's proprietary gene-silencing technology called RNAi, or RNA interference. Discovered by scientists in the late 1990s, RNAi is a natural process in which cells turn off, or silence, the activity of specific genes. ALN-AT3 silences certain genes associated with AT generation, "switching off" the protein's production.

At the XXIV Congress of the International Society on Thrombosis and Haemostasis, June 29-July 4, in Amsterdam, Alnylam shared preclinical data from animal trials. The studies revealed that ALN-AT3 improved thrombin generation in mice and nonhuman primates.

Codeine and Kids

FDA warns of life-threatening reactions after tonsillectomy and/or adenoidectomy

Surgical removal of adenoids and tonsils in kids with sleep apnea is often accompanied by a prescription for codeine to relieve the pain afterward. But not anymore. The Food and Drug Administration (FDA) added a black box warning to codeine-containing pain relievers for children after this surgery because of the risk of breathing problems and death. The warning does not apply to children who are receiving codeine for other reasons. This is important news for parents of children with bleeding disorders who may be candidates for combined adenoid/tonsil removal.

Codeine is a narcotic often paired with acetaminophen to relieve pain. It is also found in cough and cold preparations. It is broken down by an enzyme in the liver, which converts it to morphine. Some people have a genetic variation of the enzyme that causes them to metabolize codeine more quickly and fully than others. These so called "ultra-rapid metabolizers" wind up with too much morphine in their bloodstream, which can suppress breathing and lead to death.

The FDA strongly advises against using codeine in all kids after adenoid and/or tonsil surgery. If your child is scheduled for this type of surgery, talk to the surgeon about alternatives to codeine for post-op pain management. Your hemophilia treatment center may also be able to advise you on more suitable pain medications.

Excerpt of article by Sarah Aldridge, Hemaware, Summer 2013, Vol. 18, Issue 3.

which utilizes "gene silencing" technology!

Alnylam plans to file an investigational new drug application for ALN-AT3 in late 2013. It will initiate a Phase I clinical trial in humans in early 2014.

"We are very pleased that the FDA has granted Orphan Drug Designation for ALN-AT3 now for both the treatment of hemophilia A and hemophilia B. As a subcutaneously delivered RNAi therapeutic, we believe it represents an innovative approach for the management of hemophilia and has great potential to make a meaningful impact in the treatment of this often debilitating bleeding disorder," said Saraswathy (Sara) Nochur, PhD, Senior Vice President, Regulatory Affairs and Quality Assurance at Alnylam. "ALN-AT3 is a key program in our 'Alnylam 5x15' product development and commercialization strategy, and we look forward to advancing this promising RNAi therapeutic into the clinic in the months to come."

Sources: The Wall Street Journal, August 14, 2013, and Alnylam news release dated August 20, 2013

Event News

Men's Retreat

Seven men of varying ages and as many other guests participated in KHF's Men's Retreat at Cedar Ridge Camp and Retreat Center on the outskirts of Louisville on a sunny weekend in May. Cedar Ridge features a scenic country setting with an array of outdoor activities and basic but comfortable accommodations. In addition to educational presentations on "Joint Health" and "Resiliency in Aging," participants enjoyed zip lining across the lake, navigating the team challenge course, a pizza outing to Bearno's, cooking their own breakfasts, and bonding in between activities.

Fall 2013 Scholarship Awards

The Herb Schlaughenhoupt, Jr. Memorial Scholarship was awarded to Kevin Loeser of Louisville who attends the University of Louisville as a freshman this fall majoring in Business/Sports Management. Kevin is the son of Ronnie and Myra Loeser and the grandson of Herb Schlaughenhoupt, Jr. This scholarship was established in memory of Mr. Schlaughenhoupt, who is one of the founders of KHF.

The Terry D. Turner Memorial Scholarship was awarded to Kirk Bibelhauser of Versailles, a recent graduate of Woodford County High School, who now attends Bluegrass Community and Technical College in Lexington. Kirk is the son of Karen Bibelhauser and brother of Mark Bibelhauser. The Terry D. Turner scholarship was established by Nancy Cutrell of Evansville, IN in memory of her brother Terry. We are proud of Kevin and Kirk and congratulate them on their achievements.

The next submission deadline is January 15, 2014. For application form and guidelines contact KHF at 502-456-3233, 800-582-CURE (2873) or info@kyhemo.org

Kosair Gala

Representing KHF at the annual Kosair Grants Awards Gala were Glen and Debbie Hitt, Milton and Ursela Kamala, and Pete and Beverly Slapikas. This event commemorated Kosair Charities' 90th anniversary and announcement of grant awards for this year.

KHF received a $25,000 grant in support of its programming for children with bleeding disorders.

Event News

Summer Family Event & Annual Meeting

The Summer Family Event at the Seelbach Hilton in downtown Louisville attracted over one hundred attendees who participated in educational sessions, perused exhibits by pharmaceutical and home care companies, enjoyed a delicious breakfast and lunch, and mixed and mingled at a relaxed bowling get-together at Vernon's Bowling Lanes afterwards. Children's activities allowed parents to focus on the topics at hand, ranging from "Express Yourself" and "Positive Assertiveness" to "Legislative Advocacy Training" and "Turning Challenges into Choices" and to meet other families. The door prize drawing of concert tickets to American Idol Live and the Bruno Mars Concert elevated the excitement during lunch and bowling. As Lady Luck would have it, members of the Keith family from Mt. Washington won both sets of tickets.

At this event, KHF thanked outgoing board members and introduced the slate of new and continuing members and officers of the KHF Board of Directors. New officers are Lindsay Martin, CPA, President; Pete Slapikas, Vice-President; Rebecca Daigrepont, Treasurer; and Liz Hart, Secretary. KHF also recognized its most generous individual supporters, Mr. & Mrs. Terry Forcht from Corbin, Kentucky. The KHF Summer Family Event was supported in part by an educational grant from Novo Nordisk. Exhibitors included Baxter BioScience, Bayer HealthCare, Grifols, Accredo, Biogen Idec, CSL Behring, CVS Caremark, HPC Specialty Pharmacy, Kedrion BioPharma, Matrix Health, Novo Nordisk, Octapharma, Paragon Hemophilia Solutions, Pfizer, and Walgreens Infusion Services.

Upcoming Events

- **Poinsettia Sale**
- **2013 Christmas Party**
- **Vegasville 2014**

More News

Pledges for the Future of KHF

Kentucky Hemophilia Foundation's 7th Annual Fund Drive, concluded in 2013. We thank the following individuals and companies for their generous support.

Challenge Gift, $25,000+
Mr. & Mrs. Terry Forcht of Forcht Bancorp
Corbin, Kentucky

Fundraisers Toward Meeting the Challenge $5,000+
Strides for a Cure
3rd Annual KHF Relay Walk/Run

Forcht Challenge Donors, $1,000+
The Community Foundation of Louisville
made possible by the Zoeller Company
Nancy Cutrell
5th Annual Kickathon
in memory of Terry D. Turner
Don Mattingly

$500 +
David Hasch

$250 +
Patricia Ashby
Greg Browning
Chevron Humankind
First Giving
Pal Foundation
Bill Stopher

$100 +
Constellation Energy
Jewel & Cathy Daugherty
Robert Deitel
Greg Fiscus
Curt E. Flock
Fred & Darline Hartman
Hebron Presbyterian Church
Dona W. Heil
in honor of Clark & Sally Rhea
Glen & Deborah Hitt
The Humana Foundation
Betty Humphrey
Michael & Catherine Johnson
Ann Mancini
R. Dale & Kathleen Nichols
Oxmoor Hundai
Keith Peterson
The Prudential Foundation
Royce Rogers
Charles J. Schroering
Andrew Stone
Cal & Nita Zehnder

$50 +
Wanda Bandy
Paula Bias
William T. Bosserman
Sandy Franklin
GE United Way Campaign
Evan Hammett
Mary Marasa
G. Myers Trucking
in honor of Quentin Sturgill
Pete & Bev Slapikas
Woman of Immanuel-
Immanuel UCC
Gail Yates
Ann T. Young
in memory of Ben Turley Young

Up to $49
Active Network
Joe Nell Ballantine
Odie & Janet Eaves
Lisa Mattingly
Leah McCollum
Carolyn C. Metcalf
Charles & Cheri Music
Clark & Sally Rhea
in honor of Fred Heil
Michael J. Ryan
David & Georgia Wilson

More News

2012 – 2013 Kentucky Hemophilia Foundation Membership

We thank all of the members of the Kentucky Hemophilia Foundation for their support during the 2012 – 2013 program year

Individual/Family Memberships, $20+
Danny & Maritza Adams
Sara Ceresa
Sue Donahue
Susan Geralds
Janet Goff
Barbara Hendrix
James P. Huff
Frances Joyce Lewis
for Spalding Grayson
Mike Marlier

Supporting Memberships, $35+
Margaret J. Baird
Scott P. Davis
Judy Hayes
in memory of Michael Jason Hayes
Stan & Evelyn Kramer
Terrence & Caroline Loeser
David & Terry Moore
John & Carol Nord
Keith Peterson
Mary Ellen Ritchie
Clara Wheatley

Patron Memberships, $50+
Larry G. Bandy, Sr.
Karen Juett Butcher
Barbara W. Grayson
Arthur Hackman
Thomas & Alice Hendrix
David & Leslie Houvenagle
Michael Johnson
Lindsay C. Martin
The Webb Family
April Johnson Zimmerman

Sustaining Memberships, $100+
John & Leah Graham
Dianne Hardman
Eric & Venus Marcum
John & Pat Tharp
Kim Wearsch
Cal & Nita Zehnder

Benefactor Memberships, $250+
Glen and Deborah Hitt

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

Donations for the Continuation of our Herb Schlaughenhoupt, Jr. Memorial Scholarship
January 1, 2013-June 30, 2013
$500+
George Schlaughenhoupt

In Memory

January 1, 2013 – June 30, 2013

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

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

Spalding Grayson
28th memorial anniversary
Frances Joyce Lewis

Marian Turner, RN
Steven & Laura Koenig

Kathleen Kearns
Norma & Walter Hall
Ruth & Charles Hall

TOP 11

Top 11 Supporters for Fiscal Year Ending June 30, 2013

$35,000+
Baxter BioScience
Terry & Marion Forcht of Forcht Bancorp

$25,000+
Kosair Charities

$15,000+
Pfizer
Novo Nordisk

$12,000+
CSL Behring

$9,000+
Biogen Idec
Bayer HealthCare

$5,000+
CVS Caremark
Grifols
WHAS Crusade for Children

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**.

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.

KOSAIR CHARITIES
Protecting the Most Precious Gift of All

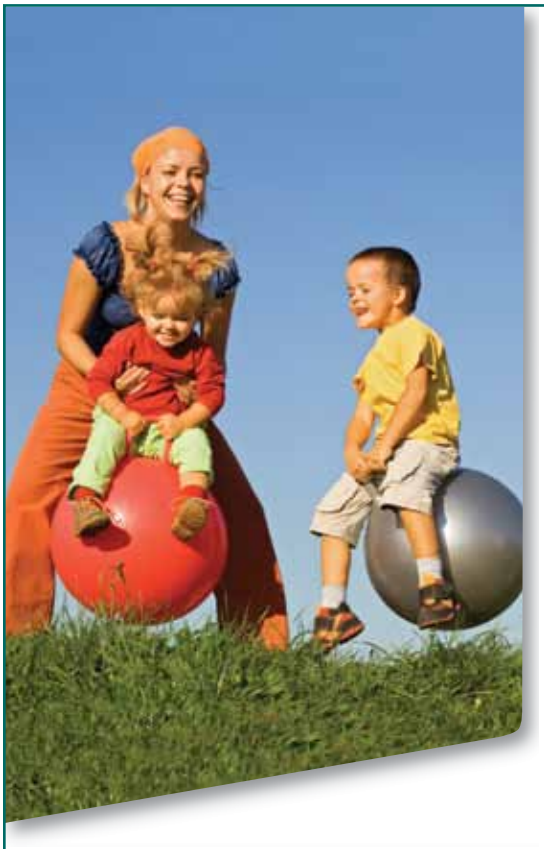
WHAS CRUSADE FOR CHILDREN

A Proud Member of
Community Health Charities®
Kentucky
WORKING FOR A HEALTHY AMERICA

COLONEL HONORABLE ORDER OF KENTUCKY COLONELS COMMONWEALTH OF KENTUCKY

KENTUCKY HEMOPHILIA FOUNDATION
1850 Taylor Avenue #2
Louisville, KY 40213-1594

Non Profit Org.
U.S. Postage
PAID
Louisville, KY
Permit No. 883



Biotherapies for Life™

CSL Behring is committed to saving lives and improving the quality of life for people with rare and serious diseases worldwide. We offer the industry's most robust product portfolio delivering "Biotherapies for Life." Through our continued focus on innovation, we are leaders in developing new and enhanced plasma-derived and recombinant biotherapies, with a 100-year heritage of quality and safety.

CSL Behring

CSL Behring LLC, P.O. Box 511, Kankakee, IL 60901 USA | www.CSLBehring.com

AlphaNine® SD
Coagulation Factor IX (Human)

Packaged with Mix2Vial® Filter Transfer Set

Available in the following potencies and color coded assay ranges

Potency	Diluent Size
500 IU FIX Range	10 mL
1000 IU FIX Range	10 mL
1500 IU FIX Range	10 mL

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 Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

GRIFOLS a new era begins
www.grifolsusa.com

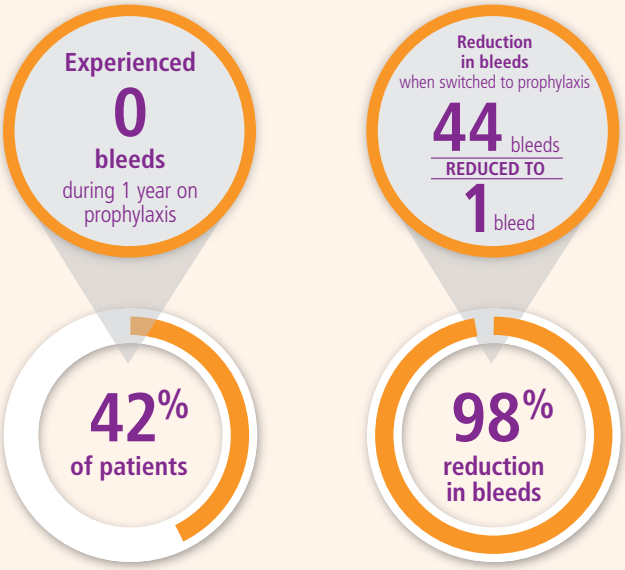
Baxter

UNLOCKING SELF-POTENTIAL

PROPHYLAXIS WITH ADVATE REDUCED BLEEDS IN A CLINICAL STUDY[1,a]

ADVATE is the only recombinant factor VIII (eight) that is FDA approved for prophylaxis in both adults & children (0-16 years)[1]

Significant reduction in median annual bleed rate (ABR) with prophylaxis treatment compared with on-demand treatment[1,a]



- 0 bleeds experienced by 42% of patients during 1 year on prophylaxis[1,a]
- 98% reduction in median annual bleed rate (ABR) from 44 to 1 when switched from on-demand to prophylaxis[1,a]
- 97% reduction in joint bleeds from 38.7 to 1 after switching from on-demand to prophylaxis[1,a]
- No subject developed factor VIII inhibitors or withdrew due to an adverse event (AE)[2,a]

[a]In a clinical study, after switching from 6 months of on-demand treatment to 12 months of prophylaxis with ADVATE in 53 previously treated patients with severe or moderately severe hemophilia A.

Ask your healthcare provider if prophylaxis with ADVATE is right for you.

Detailed Important Risk Information for ADVATE

You should not use ADVATE if you are allergic to mice or hamsters or any ingredients in 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 and dietary supplements, have any allergies, including allergies to mice or hamsters, are nursing, are pregnant, or have been told that you have 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.

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.

Side effects that have been reported with ADVATE include: cough, sore throat, unusual taste, abdominal pain, diarrhea, nausea/vomiting, headache, fever, dizziness, hot flashes, chills, sweating, joint swelling/aching, itching, hematoma, swelling of legs, runny nose/congestion, and rash.

Call your healthcare provider right away about any side effects that bother you or if your bleeding does not stop after taking ADVATE.

Indication for ADVATE

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is a medicine used to replace clotting factor VIII 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.

Please see Brief Summary of ADVATE Prescribing Information on the next 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.

References:

1. ADVATE Prescribing Information. Westlake Village, CA: Baxter Healthcare Corporation; July 2012. **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. *J Thromb Haemost*. 2012;10(3):359-367.

ADVATE
[Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]
There's more to life.

www.advate.com | 888.4.ADVATE

ADVATE
[Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]
Brief Summary of Prescribing Information. Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Control and Prevention of Bleeding Episodes

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is an Antihemophilic Factor (Recombinant) indicated for control and prevention of bleeding episodes in adults and children (0-16 years) with Hemophilia A.

Perioperative Management

ADVATE is indicated in the perioperative management in adults and children (0-16 years) with Hemophilia A.

Routine Prophylaxis

ADVATE is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children (0-16 years) with Hemophilia A.

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

CONTRAINDICATIONS

Known anaphylaxis to mouse or hamster protein or other constituents of the product.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible and have been reported with ADVATE. Symptoms have manifested as dizziness, paresthesias, rash, flushing, face swelling, urticaria, dyspnea, and pruritus. *[See Patient Counseling Information (17) in full prescribing information]*

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG): maximum of 0.1 ng/IU ADVATE and hamster proteins: maximum of 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

Carefully monitor patients treated with AHF products for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs). 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 (5.3) in full prescribing information]*

Monitoring Laboratory Tests

The clinical response to ADVATE may vary. If bleeding is not controlled with the recommended dose, determine the plasma level of Factor VIII and administer a sufficient dose of ADVATE to achieve a satisfactory clinical response. If the patient's plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, suspect the presence of an inhibitor (neutralizing antibodies) and perform appropriate tests as follows:

- 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 (2) in full prescribing information]*
- 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 drug reactions (ADRs) seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to Factor VIII.

The most common ADRs 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 studies in previously treated patients (PTPs) and one ongoing study 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 128.0 (range: 1 to 598).[1]

The summary of adverse reactions (ADRs) with a frequency ≥ 5% (defined as adverse events occurring within 24 hours of infusion or any event causally related occurring within study period) is shown in Table 1.

No subject was withdrawn from a study due to an ADR. There were no deaths in any of the clinical studies.

IMMUNOGENICITY

The development of Factor VIII inhibitors with the use of ADVATE was evaluated in clinical studies 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 (2.0 [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).[1,2] No Factor VIII inhibitors were detected in the 53 treated pediatric PTPs.

In clinical studies 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.[1] Four patients 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 patients, 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.

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 2 represents the most frequently reported post-marketing adverse reactions as MedDRA Preferred Terms.

Table 1
Summary of Adverse Reactions (ADRs)[a] with a Frequency ≥ 5% in 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] ADRs 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 study in PUPs as of 27 March 2006.

[c] MedDRA version 8.1 was used.

Table 2
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.

References: 1. 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 9:273-283. **2.** Tarantino MD, Collins PW, Hay PW et al. 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 10:428-437.

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-873-2838.

Baxter Healthcare Corporation, Westlake Village, CA 91362 USA

U.S. License No. 140 Printed in USA Issued July 2012

Baxter

Pfizer Hemophilia

You may be eligible for a FREE 1-month supply up to 20,000 IU of factor* from Pfizer Hemophilia

Go to www.FreeTrialHemophiliaA.com or www.FreeTrialHemophiliaB.com, download the discussion guide, and bring it to your next health care provider visit.

*Terms and conditions apply. Visit www.hemophiliavillage.com for complete terms and conditions. You must be currently covered by a private [commercial] insurance plan. For questions about the Pfizer Hemophilia Trial Prescription Program, please call 1.800.710.1379 or write us at Pfizer Hemophilia Trial Prescription Program Administrator, MedVantx, PO Box 5736, Sioux Falls, SD 57117-5736. If you are not eligible for the trial prescription program, you may find help accessing Pfizer medicines by contacting Pfizer's RSVP program at 1-888-327-RSVP (7787).

Wyeth® Manufactured by Wyeth Pharmaceuticals Inc.

Marketed by Pfizer Inc.

10% TOTAL RECOVERED FIBER

Printed in USA/June 2012

BAYER HEALTHCARE AND THE HEMOPHILIA COMMUNITY:

Commitment, Leadership *and* Innovation

Bayer HealthCare

Printed in USA KN10001111

AlphaNine® SD
Coagulation Factor IX (Human)

Packaged with Mix2Vial® Filter Transfer Set

Available in the following potencies and color coded assay ranges

Potency	Diluent Size
500 IU FIX Range	10 mL
1000 IU FIX Range	10 mL
1500 IU FIX Range	10 mL

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 Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

GRIFOLS a new era begins
www.grifolsusa.com

Pfizer Hemophilia

You may be eligible for a FREE 1-month supply up to 20,000 IU of factor* from Pfizer Hemophilia

Go to www.FreeTrialHemophiliaA.com or www.FreeTrialHemophiliaB.com, download the discussion guide, and bring it to your next health care provider visit.

*Terms and conditions apply. Visit www.hemophiliavillage.com for complete terms and conditions. You must be currently covered by a private [commercial] insurance plan. For questions about the Pfizer Hemophilia Trial Prescription Program, please call 1.800.710.1379 or write us at Pfizer Hemophilia Trial Prescription Program Administrator, MedVantx, PO Box 5736, Sioux Falls, SD 57117-5736. If you are not eligible for the trial prescription program, you may find help accessing Pfizer medicines by contacting Pfizer's RSVP program at 1-888-327-RSVP (7787).

Wyeth® Manufactured by Wyeth Pharmaceuticals Inc.

Marketed by Pfizer Inc.

10% TOTAL RECOVERED FIBER

Printed in USA/June 2012

I will take control of my VWD

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

wilate®

The Power to Control VWD

www.wilateusa.com

Important Safety Information:

wilate® is contraindicated for individuals with a history of anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapies. FVIII activity should be monitored to avoid sustained excessive FVIII levels. wilate® is made from human plasma. The risk of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease agent, cannot be completely eliminated. The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions.

Please see the Highlights of Prescribing Information on the adjacent page.

Date of preparation 04/13. WIL-026-CAD

To report suspected adverse reactions,contact:

Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

octapharma
For the safe and optimal use of human proteins

octapharma
For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Wilate safely and effectively. See full prescribing information for Wilate.

Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human), Powder for Solution, for Intravenous Use Only. Initial U.S. Approval: 2009

INDICATIONS AND USAGE

- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is also not indicated for Hemophilia A

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

CONTRAINDICATIONS

- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reaction
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients
- Theoretical risk of infectious agents transmission as the product is made from human plasma

ADVERSE REACTIONS

The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.**

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

Type of Hemorrhages	Loading Dosage (IU VWF:RCo/kg BW)	Maintenance Dosage (IU VWF:RCo/kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12 – 24 hours*	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12 – 24 hours*	VWF: RCo and FVIII activity through levels of >50%

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

NDC Number	Size	Protein Amount
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

HOW SUPPLIED/STORAGE AND HANDLING

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.

Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstitute the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.

Manufactured by:

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria
U.S. License No. 1646

Distributed by:

Octapharma USA Inc.
121 River Street, 12th floor
Hoboken, NJ 07030

octapharma
For the safe and optimal use of human proteins

BAYER HEALTHCARE AND THE HEMOPHILIA COMMUNITY:

Commitment, Leadership *and* Innovation

Bayer HealthCare

Printed in USA KN10001111