FALL 2012

RMHBDA Newsletter

The Rocky Mountain

Rocky Mountain Hemophilia & Bleeding Disorders Association

RMHBDA is a 501(c)(3) nonprofit organization founded in 2000 and is a chartered chapter of the National Hemophilia Foundation.

Our mission is to improve the quality of care and life for persons with inherited bleeding disorders, including hemophilia and von Willebrand Disease through education, peer support, resources, and referral.

In This Issue

RMHBDA Education Weekend 2013

February 22–24

Our Education Weekend will take place at the Hilton Garden Inn in Bozeman.

We need help organizing!

Please contact Brad at 406.600.2554 if you are interested in serving on the Education Weekend committee.

This is your organization!

Family Camp 2013

June 14 - 16

Each summer, RMHBDA invites affected families living in Montana and Wyoming to attend a weekend retreat. The weekend is packed full of education, bonding, and fun!

This year will be at Luccock Park Camp, Livingston, Montana in Paradise Valley; for more information, visit www.luccock.org

For the parents and teens, we will have teambuilding programming led by our guest, hemophilia leadership expert, Pat Torrey (www.patricktorrey.com) and some time to relax with other families. This is a great opportunity to learn from and share experiences with one another.

We also have many great activities planned for our campers including arts & crafts projects, field games, and educational sessions for children with bleeding disorders and their siblings. Infusion classes will be offered from HTC RN, Sue Geraghty. Call Brad with any questions at 406.600.2554

From Our Executive Director

We couldn't have asked for a nicer day on September 8, 2012. We had over 125 walkers at our First Annual Walk for Hemophilia at Bogert Park in Bozeman, Montana. Good natured and generous supporters helped raise over $41,000 and awareness at our first ever walk. I want to send a very gracious thank you to our volunteers, team captains, and walkers for making our walk a tremendous success. We are so grateful for your participation.

We would also like to extend a very gracious thank you to our local and corporate sponsors: Barnard Construction, Baxter, Bayer, Biogen Idec, Bozeman Deaconess Health Services, CSL Behring, Fifth Street Design, First Interstate Bank, Grifols, HF Healthcare, Insty Prints, Novo Nordisk, Pfizer, and Restore RX.

See more photos on page 2, *and visit our Facebook page for all of the wonderful photos of our First Annual Walk! (www.facebook.com/rmhbda)*

Sincerely,
Brad Benne,
Executive Director

Rocky Mountain Hemophilia & Bleeding Disorders Association

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Walk Photos

The First Annual Walk was a fantastic success raising over $41,000 and raising awareness of RMHBDA and of blood disorders to the public. It was also wonderful fun with a great turnout as you can see on these pictures.

We also wish to honor and thank our top fundraisers and teams!

Top Fundraisers

1. Susan & Brad Benne
2. Chris Graham
3. Lisa Maxwell
4. Forrest Berg
5. Campbell Hunter
6. Heidi Hart
7. Mary Ann Ludwig
8. Craig Akers
9. Connor Ferriter
10. Dylan Rosa Hunter
11. Kristal Graham
12. Jessica Amende
13. Ann Arthur
14. Spencer Straub
15. Kevin Amende
16. Scott Maxwell
17. Lane & Dylan Maxwell
18. Kevin Brustuen
19. Sean Jeffrey
20. Sara Jestrab

Top Teams

1. Blood Brothers
2. Max Limp
3. The "Non-walkers"
4. Best of the Bleed
5. The Warriors
6. Cam's Papa
7. Tough Enough To Bleed!
8. Clot Like an Amende
9. Kotex's Best Customers
10. Connor's Comrades
11. Globe Clotters
12. Friends of Blood
13. Team Activate to Coagulate
14. Walgreens Infusion Services
15. Grandma Jane
16. St Vincent Children's Healthcare
17. Biogen Idec Hemophilia
18. Ellison Family
19. HemTeam

National Hemophilia Foundation and Rocky Mountain Hemophilia and Bleeding Disorders Association Present
HEMOPHILIA walk '12
Every step makes a difference
National Presenting Sponsor Baxter

RestoreRx
Congrats on your successful walk!

See many more and larger versions at

www.facebook.com/rmhbda.

Getting in the Game 2012

Hi my name is Avery Amende, and this year I went to Texas to play golf for our chapter. Luckily, my brother Wyatt Amende got chosen to come play baseball, so he got to share this really amazing opportunity with me. There is so much worth sharing about our great trip, but the one thing I want to get across to you all is how important fitness, and activity needs to play a part in our lives, especially for those who have hemophilia or some sort of bleeding disorder. On our trip, there was a lot of talk about how important sports are, and how to treat yourself if you are hurt or wounded. Thankfully, nobody that I knew of got hurt!

Perry Parker was the professional golfer who guided us through everything, and he really helped me get ready for the tournament the next day. On the Saturday of our trip, we had our tournament. I was very lucky on the tournament, because I got a super nice caddy! I think he definitely helped me with technique and patience. I went along with two other kids on the golf course, and we each did very well! At the award banquette that night, I got the "longest drive" award, and a very good score that I will now try to beat!

I want to thank our chapter for sending my brother and I to Texas for this great event. This was a very fun trip, and it helps me realize that no matter what kind of person I am, I can always push myself to do something that makes me more fit, and happy!

This year I (Wyatt Amende) flew to Dallas to represent my chapter in the 11th ever Gettin' in the Game baseball and golf competition. Throughout the weekend I was able to enhance my skills in major portions of the sport, pitching, fielding, and hitting. I felt the experience would have been majorly different had the athletes Jessie Schrader, Ivan Sada, and Peter Dyson not been involved. But even more importantly than the sport, I think the social experience was even better. I met 2 new friends from completely different parts of the United States. One was from Hawaii and the other was from Ohio. I'm really thankful that my chapter has given the opportunity for me to travel to participate in this big event, and I hope I can return next year.

The Carrier Barrier

Women Push for Mild Hemophilia Diagnosis

By Sarah Aldridge | 07.19.2012

Reprinted with permission from the National Hemophilia Foundation

They experience similar bleeds and bruises as men with mild hemophilia, yet they're called "symptomatic carriers." For women, that label is confining and confounding. It also places their health at risk.

"Using the term 'symptomatic carrier' doesn't validate us," says Tammy Davenport, 38, of Kingwood, Texas, a regional ¬coordinator for Matrix Health. "We have very different issues than men, but they're no less severe." Daven-port's father had hemophilia A and had her tested for it when she was 5. Her factor VIII (FVIII) assay was 23%. The doctor told her parents, "She has mild ¬hemophilia. If she ever has any surgeries or accidents, she may need factor."

However, that news did no good when Davenport went into labor with her son in 1994. "I went into the hospital explaining that I had hemophilia, and they needed to be aware of that," she says. The doctors told her, "That's impossible. Women can't have it." Consequently, they ordered no factor product. Davenport developed a large hematoma with a golf ball-sized knot on her spine from the epidural. It took a year to heal.

The burden for women whose concerns are discounted is both physical and emotional. When their bleeding symptoms are undertreated, they experience health complications. When their concerns are brushed aside, they feel frustrated and angry, losing confidence in the medical community.

But women are finding ways to get around the carrier barrier. Through advocacy and education, patients and providers are pushing for recognition of mild hemophilia.

"Carrier" Confusion

In genetics, a carrier is typically defined as a person who has a genetic mutation for a disease that can be passed on to a child, but who doesn't have symptoms. But for hemophilia, the label "symptomatic carrier" describes a woman who not only has the mutation but also has symptoms.

"I want to clarify this terminology because people get this confused all the time," says Marion A. Koerper, MD, medical adviser of the National Hemophilia Foundation (NHF). She is also director emerita of the HTC at the University of California, San Francisco, where she practices pediatric hematology. "Being a carrier is a genetic designation, not a diagnosis. It says nothing about how you are clinically."

Clinical information is partially provided by measuring the factor level. "Regardless of whether you're male or female, if your factor FVIII (FVIII) or factor IX (FIX) level is below 49%, you can have bleeding symptoms," Koerper says. "You have mild hemophilia."

The hemophilia diagnosis can be confirmed by genetic studies. "As genetic testing is becoming more available, particularly gene mutation analysis, it's becoming increasingly helpful," says Steven W. Pipe, MD, medical director of the Pediatric Hemophilia and Coagulation Disorders Program at the University of Michigan, Ann Arbor. For a woman with no family history of hemophilia, the lab can analyze her DNA for the most common FVIII mutation, the intron 22 inversion, a reversal of a section of DNA. It accounts for 40%–50% of cases of severe hemophilia A. "We've identified some women from that second-step testing," Pipe says.

The concept that women can't have hemophilia needs to be corrected. "That's a misconception that we probably have to devote some more attention to for education and outreach purposes," Pipe says. "If they have bleeding symptoms that can be managed with the interventions we have available, then they should be considered as having a mild bleeding disorder."

According to NHF, the normal plasma levels of FVIII range from 50% to 150%. Mild hemophilia is defined as having a FVIII level of 6%–49%. Because women have two X chromosomes, the level of FVIII they produce depends on the balance between the normal X chromosome and the abnormal one carrying the hemophilia gene. If the balance is equal, the FVIII level would not typically be lower than 50%.

"If the greater proportion of their FVIII level is dependent on the mutant FVIII gene, their factor levels can clearly be in the low range," Pipe says. Additionally, some carrier women with FVIII levels as high as 50%–60% may still experience bleeds.

Symptoms: Missed and Dismissed

Mild hemophilia's trademark symptoms—bruising, nosebleeds, heavy menstrual periods (menorrhagia), and prolonged bleeding after trauma or dental or surgical procedures—can be missed or dismissed in girls and women. Danielle and Heather Schwager, 25, twins from Strongsville, Ohio, had symptoms during childhood. "We were kids who grew up playing outside all the time, and we were always bruised," says Danielle. The twins' mother, Vickie, a neonatal nurse practitioner, periodically questioned the pediatrician, wondering if her daughters had hemophilia B, like her father. "He kept telling me, 'No, females don't have hemophilia,'" Vickie says.

Five years later, Danielle bled for 10 days after having four teeth pulled. Her oral surgeon and orthodontist sensed something amiss and referred the family to the hemophilia treatment center (HTC) in Cleveland. Factor level testing confirmed Vickie's hunch. "My factor level was about 8% or 9% when I was diagnosed with mild hemophilia B," says Danielle. Heather's was about 40%. Those diagnoses took more than a decade.

During NHF's Annual Meeting in Chicago in November 2011, Koerper and Vickie conducted an educational session for women with mild hemophilia. Many women recounted similar experiences. "These women know they're bleeding too much," Koerper says. But their doctors disregarded their concerns, saying: "You got a big bruise because you banged your leg." Problems result when a surgery is performed without a treatment plan. "They'll have their gallbladder out, and then they have bleeding complications," says Koerper.

Davenport warned her new hematologist, who was inexperienced in treating women with bleeding disorders, that her factor level might soar from the stress she was feeling before a hysterectomy, but then would plummet afterward. Because her factor level skyrocketed to 80%, the hematologist took no precautions. Davenport woke up in the recovery room hearing her doctor tell the staff, "I don't know what's causing her bleeding. She doesn't have hemophilia."

"When they call you a 'symptomatic carrier,' and that's your label, you tend not to be treated seriously," Davenport says. For her, that resulted in post-op bleeding. For others, it might mean joint damage and arthritis from untreated bleeds or serious complications following childbirth.

Emotional and Behavioral Toll

The emotional and behavioral consequences for women with mild hemophilia who perceived errors in their medical care were documented in a 2011 study in Haemophilia by Nisa Renault and researchers at Dalhousie University in Halifax, Nova Scotia, Canada. The 11 women interviewed cited 264 negative emotional responses, including anger, doubt and mistrust.

A doctor's disbelief can lead to a patient's disillusionment. "It is frustrating to try to explain this to physicians who I would expect to know something about bleeding disorders," says Vickie.

Davenport was devastated when her doctor denied that she had hemophilia after her hysterectomy. "It was very hard on me to doubt the fact that maybe I believed this for 35 years, and it just wasn't right," she says. The pain went deep, as Davenport lost a comforting family connection. "That took away my identity—all I had of my dad."

Perceived mistreatment by healthcare providers also produced negative behavioral responses in the Canadian study subjects. Some women minimized the importance of their symptoms. Others avoided conflict by finding a new doctor or treatment center. Some were so desperate that they treated themselves with factor product they borrowed from a family member. However, this practice is not recommended and may even be dangerous. The borrowed medication may be the wrong dosage or wrong medication entirely from what your physician would have prescribed, says Pipe.

Advocacy in Action

A positive behavior that emerged among women in the Canadian study was to advocate for themselves or others. Some insisted on in-depth testing or better treatment, or seeking another opinion.

When Davenport needed emergency gallbladder surgery, she chose a smaller hospital closer to home. There she found an understanding hematologist. "He said, 'Okay, you seem to know what you're talking about,'" says Davenport. "He went with my history, not my labs." She brought in factor and saw the hematologist three times before the procedure. "I was on prophylaxis for a week out," Davenport says. "I had zero bleeding problems."

Vickie and Danielle are involved in local advocacy through the Northern Ohio Hemophilia Foundation in Cleveland. "Our local task force set up a program for dental professionals to make sure that they were educated on women's bleeding disorders," says Vickie. Further, the chapter has invited gynecologists and obstetricians to evening meetings to educate them. Danielle put together a brochure for the chapter to raise awareness about women's bleeding disorders. Both are on NHF's Women's Task Force, broadening their advocacy reach.

Critical Role of the HTC

Building a relationship with your HTC is critical for women with bleeding disorders. "Primary care physicians don't always understand the nuances of the testing," says Koerper. They may order the standard screening tests, see that the partial thromboplastin time [PTT, a measure of clotting time] is within normal range, and tell women they're fine, she says. "They don't understand that they have to order the actual FVIII or FIX activity test." The HTC can also order further tests to pinpoint the mutation. A 2011 study in Haemophilia showed that a woman's mutation, not factor level per se, was a better predictor of bleeding. (See "Test Takers," *HemAware* Fall 2011; "What's Your Genotype?" *HemAware* Spring 2010.)

Once you receive a mild hemophilia diagnosis from your HTC, you can get the benefits of comprehensive care. "We can offer them the same things we do for men with mild hemophilia, guidance around procedures and hemostatic support if necessary," Pipe says. "We can help them with their family planning."

Prior to surgery or dental procedures, your HTC can create a treatment plan to prevent or stop bleeding, which the dentist or surgeon can follow. "They were very aggressive with my treatment when I had dental work," says Davenport of the staff at her son's HTC. "I was on prophy, and everything was taken care of."

Treatment centers can also help untangle insurance hassles. Their experience with medical coding can make all the difference. "They have to use the appropriate code on every single encounter with you and for any treatment you need, such as factor, so that the insurance company will pay for it," Koerper says.

Without the diagnosis, the "carrier" label may be interpreted to mean you are asymptomatic. "A genetic designation does not equal a diagnosis," says Koerper. "To an insurance company, it means nothing." The Schwagers discovered that the hard way. "With the 'symptomatic carrier' label, we run into a lot of insurance issues. They see my birth control pills as contraception and an optional medication," Danielle says. At times, the insurer has denied her coverage.

Mild Hemophilia: Not for Men Only

Mild hemophilia should no longer be a "for men only" diagnosis, says Davenport. "If you have the symptoms of a disease or disorder and you have the labs to prove it, then you have it. It doesn't matter what your gender is."

Danielle has fully accepted her diagnosis and identity. "When I identify myself, I say, 'I am a woman with mild hemophilia. I am a woman with hemophilia B.'"

2013 Calendar of Events & Programs

Tentative

The chapter is still determining exact dates for several programs and events for the community. Program dates still pending include: Women's Yellowstone Adventure, Men's Retreat in potential conjunction with Snake River Hemophilia Association, and CSL's Getting in the Game Program

January 2013

13–15 NHF National Walk Training

24–26 NACCHO Camp Conference

February 2013

22–24 RMHBDA Education Weekend in Bozeman

27–March 1 NHF Washington Days

March 2013

Hemophilia Awareness Month!

April 2013

17 World Hemophilia Day:

25–27 HFA Annual Symposium

May 2013

14–15 Walk "Call to Action" Meeting (Bozeman & Billings)

June 2013

14–16 RMHBDA Family Camp (Luccock Camp Park, Livingston, MT)

July 2013

12–14 Mile High Summer Camp Leadership Pre-camp Retreat

TBA Minor League Baseball Night: Cheyenne, Missoula &Billings **(Pending Funding)**

14 – 19 Mile High Summer Camp (Rocky Mountain Village, Empire CO)

29 – Aug 2 Women's Yellowstone Adventure (Yellowstone Park) **(Pending Funding)**

August 2013

17–18 Walk Kickoff Event in Bozeman & Billings

September 2013

TBA Walk for Hemophilia, Bozeman (**Pending MSU Football sched & park availability**)

October 2013

3–5 NHF Annual Meeting (Anaheim)

11–13 TBA Men's Retreat (West Yellowstone) (**Pending Funding**)

December 2013:

4–5 RMHBDA Holiday Party (Bozeman & Billings)

Novo Nordisk files for Regulatory Approval of Turoctocog Alfa for Hemophilia A in the US & EU

Novo Nordisk announced on October 16, 2012, the submission of the regulatory application for turoctocog alfa (NN7008) to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Turoctocog alfa is a third-generation recombinant coagulation factor VIII intended for prevention and treatment of bleeding in people with haemophilia A.

"We are very excited about having reached this goal. Turoctocog alfa represents a new treatment alternative for people with haemophilia A and is one of the first important outcomes of the haemophilia research strategy we embarked upon in 2006," says Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk.

Turoctocog alfa demonstrates Novo Nordisk's commitment to the wider haemophilia community as the new alternative in factor VIII treatment. Based on the most advanced protein and purification technology, the product has been designed to expand reliability, safety and portability for people with haemophilia A.

The decision to apply for marketing authorisation for turoctocog alfa is based upon the results of the clinical trials guardian™1 and guardian™3, which were completed in 2011. More than 200 people with haemophilia A around the world were enrolled, making guardian™ the largest clinical pre-registration trial programme conducted in haemophilia A.

The phase 3 trials included previously treated adults and children with severe haemophilia A and demonstrated

Visit www.novonordisk.com for more information.

Biogen Idec & Sobi Announce Positive Top-Line Results for Hemophilia B

Biogen Idec and Sobi Announce Positive Top-Line Results from Phase 3 Study Investigating Long-Lasting Recombinant Factor IX Fc Fusion Protein in Hemophilia B

Prophylactic regimens resulted in low single-digit annualized bleeding rates

- Median dosing interval was 14 days in the individualized interval prophylaxis arm during the last 6 months on study
- Greater than 90% of bleeding episodes were controlled by a single injection of rFIXFc
- No patients developed inhibitors to rFIXFc
- The primary efficacy and safety objectives were met and Biogen Idec plans to submit a BLA to US FDA in first half 2013

Weston, Mass and Stockholm, Sweden — September 26, 2012 — Biogen Idec (NASDAQ: BIIB) and Swedish Orphan Biovitrum (Sobi) (STO: SOBI) today announced positive results from B-LONG, a clinical study that evaluated a new long-lasting clotting factor candidate in people with hemophilia B. Hemophilia B is a rare inherited disorder that impairs blood coagulation.

Top-line results from B-LONG, a global, multi-center, Phase 3 clinical study of the companies' long-lasting recombinant Factor IX Fc fusion protein (rFIXFc), showed that rFIXFc was effective in the control and prevention of bleeding, routine prophylaxis, and perioperative management. Recombinant FIXFc was generally well-tolerated. Additional analyses of the B-LONG study are ongoing and the companies anticipate presenting further results at a future scientific meeting.

"The results of the B-LONG study offer the potential for longer-lasting protection from bleeding for patients with hemophilia B," said Glenn Pierce, M.D., Ph.D., Senior Vice President of Global Medical Affairs and Chief Medical Officer of Biogen Idec's hemophilia therapeutic area. "Currently, prophylactic treatment of hemophilia B requires intravenous injections up to three times a week, which makes the prospect of a longer-lasting Factor IX therapy very exciting."

Visit www.rockymountainhemophilia.org to read the complete press release.

FDA Approves Advate 4000 IU Dosage Strength

The U.S. Food and Drug Administration (FDA) has approved a new 4000 IU dosage strength of Baxter's ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]. ADVATE is a full-length recombinant factor VIII (FVIII) product that is indicated for the control and prevention of bleeding episodes in patients with hemophilia A.1 The new 4000 IU dosage strength provides the convenience of a single vial dosing opportunity for many adult patients, including some patients on a dosing schedule of every three days for prophylactic treatment with ADVATE.

Baxter is the only company to offer a 4000 IU dosage. A broad selection of 11 dosages enhances convenience for patients by offering the opportunity to use a single vial rather than infusing multiple vials of therapy. The 4000 IU will be available to patients in the United States in August.

"The 4000 IU dose is particularly well-suited for patients on an every three-day prophylaxis regimen," said Bruce Ewenstein, M.D., Ph.D, vice president, clinical affairs, Baxter's BioScience business.

In December 2011, ADVATE was approved by the U.S. FDA for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A, becoming the only antihemophilic recombinant FVIII treatment approved in the U.S. for prophylactic use in both adults and children (0-16 years). The approval was based on Phase IV data showing that routine prophylaxis of ADVATE significantly reduced median annual bleed rates (ABR) in hemophilia A patients from 44 to one as compared to an on-demand regimen, a 98 percent reduction in ABR. 42 percent of patients experienced no bleeding episodes while on one year of prophylactic treatment.1

"The 4000 IU single-dose vial will be available with 5 mL diluent and may offer greater convenience for people requiring higher doses by decreasing the number of vials needed and reducing total infusion volume,"1 said Jacopo Leonardi, V.P., Sales & Marketing, U.S. Hemophilia, Baxter Healthcare Corporation. Your healthcare provider will tell you how much ADVATE to use based on your weight, the severity of your hemophilia A, and where you are bleeding. Please remember that the maximum infusion rate remains unchanged at 10 mL per minute.

To read the complete press release, visit www.baxter.com.

Learn. Explore. Connect With Our Hemophilia Community on **Facebook**.

Our Hemophilia Community

Find us on **Facebook.com/OurHemophiliaCommunity**

Printed in USA/March 2011

Pfizer

BAYER HEALTHCARE AND THE HEMOPHILIA COMMUNITY:

Commitment, Leadership *and* Innovation

Bayer HealthCare

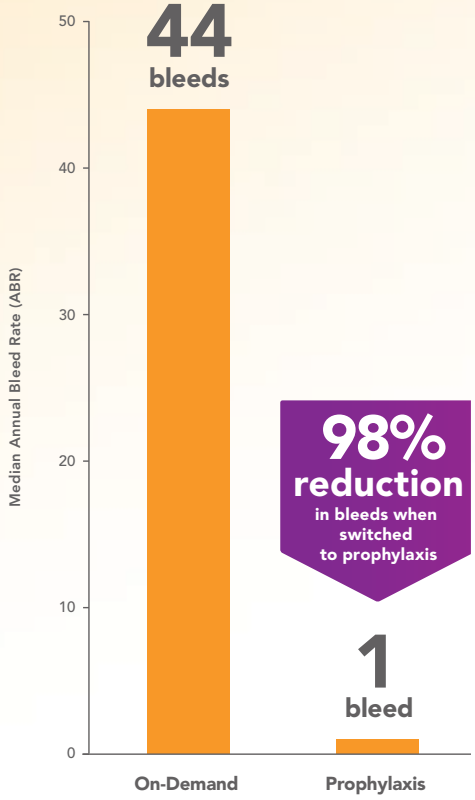
Printed in USA KN10001111

Prophylaxis with ADVATE delivers 44 to 1[1]

ADVATE IS THE **ONLY** RECOMBINANT FACTOR VIII (EIGHT) THAT IS

PROPHYLAXIS WITH ADVATE

THE POWER TO REDUCE YOUR ANNUAL BLEED RATE (ABR)



Significant reduction in ABR[1]

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:

- **Median ABR of 1** while on either prophylaxis regimen[1]
  - prophylaxis every second day (20-40 IU/kg)
  - prophylaxis every third day (20-80 IU/kg, targeted to maintain FVIII trough levels ≥1%)
- **42% of patients experienced zero bleeds** during 1 year on prophylaxis[1]
- **No subject developed factor VIII inhibitors** or withdrew due to an adverse event (AE)[4]

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 people with hemophilia A. Your healthcare provider may give you ADVATE when you have surgery.

ADVATE is not used to treat von Willebrand Disease.

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; December 2011. **2.** Helixate FS prescribing information. Kankakee, IL: CSL Behring LLC; August 2009. **3.** Kogenate FS prescribing information. Tarrytown, NY: Bayer Healthcare LLC; March 2011. **4.** 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. **5.** Maruish ME, ed. *User's Manual for the SF-36v2 Health Survey.* 3rd ed. Lincoln, RI: QualityMetric Incorporated; 2011.

TALK TO YOUR HEALTHCARE PROVIDER TO SEE HOW PROPHYLAXIS

FDA APPROVED FOR PROPHYLAXIS IN BOTH **ADULTS & CHILDREN (0-16 YEARS)**[1-3]

PROPHYLAXIS WITH ADVATE

THE POWER TO IMPROVE YOUR PHYSICAL HEALTH–RELATED QUALITY OF LIFE

Physical Component Score
Improvements in physical functioning, well-being, and energy level.[5]

Bodily Pain
Reduced levels of pain and improvements in the limitations of work due to pain.[5]

Role Physical
Improvements in the ability to perform physical activities without limitations due to health.[5]

Clinically meaningful improvements

After 12 months of prophylactic treatment, physical health–related quality of life improved in patients, mainly due to clinically meaningful improvements in*:

- the amount of pain experienced by a patient and how much pain interferes with normal work
- the impact physical health can have on performing work or other daily activities

*Clinically significant changes were not seen in the physical health–related sub-categories of General Health and Physical Functioning and the mental health–related component score and sub-categories of Mental Health, Role Emotional, Social Functioning, and Vitality.

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.

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

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

There's more to life.

advate.com | 888.4.ADVATE

WITH ADVATE CAN HELP REDUCE YOUR ANNUAL BLEED RATE (ABR)

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 informaiton]

ADVATE contains trace amounts of mouse immunoglobulin G (MulgG): 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, Monitoring Laboratory Tests]

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 any Adverse Event that occurred within 24 hours after being infused with investigational product OR all Adverse Events assessed related or possibly related to investigational product OR 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.

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