If you have been experiencing issues with your insurance company, WE WANT TO HEAR YOUR STORY!

You are not just a number; you are part of a community that cares!

Project CALLS is designed with a personal touch in mind. As a participant you will speak privately with a trained member of the HFA staff about your insurance issues. Depending on your preference, you may call the number below, send an email, or complete the form to be contacted.

Through your participation in Project CALLS, HFA will collect stories from the bleeding disorders community across the country, collate the data, identify trends, and use the information to build cases for change.

If you or a member of your family have been:

• Denied services or have received an exception,
• Forced by an insurance company to “fail” on a product before being allowed to use the product of your choice,
• Mandated to a pharmacy that is not meeting your needs, and/or
• Forced to go through a lengthy pre-/prior-authorization process,

Project CALLS is for you!

To contact us about your insurance issue, please call (202) 836-2530, email projectCALLS@hemophiliafed.org, or visit www.ProjectCALLS.org
In This Issue:

4 Executive Corner

6 Product Evolution: Decades of Innovation

9 Current Products on the Market

19 Emerging Therapies

24 Learn About Clinical Studies

27 Informed Consent: A Process, Not Just a Form

30 Oh, The Places We’ll Go! Novel Therapies for Hemophilia and Other Bleeding Disorders

32 US Food and Drug Administration’s Drug Approval Process

36 Access Challenges for New Treatments
Dear Community Members,

When my son Nicholas was born 14 years ago, gene therapy was the subject of conversation in the community, and longer-lasting factor was barely mentioned. Over the years, the emphasis seemed to flip and, for a variety of reasons, gene therapy took a bit of a back seat while new, longer-lasting factor products were introduced to the market. Recently gene therapy, along with other novel therapies such as RNAi and bi-specific antibody, have reestablished themselves as the subject most on community members’ minds.

In the fourteen years that I’ve been fortunate to have Nicholas in my life, 18 new products have been released onto the market. As a mom trying my best to navigate my child’s healthcare needs, I’ve felt that the amazing growth within the industry has added to the everyday challenges that hemo-moms and -dads face. And as the product options have changed, so too have my thoughts on those options. When Nicholas was a baby starting prophylaxis, my husband and I just wanted to find a product that worked well for him while we prayed for no inhibitor development.

Once we were several years into three-days-a-week prophylaxis, a long-lasting product came to market and I thought without hesitation that I’d want Nicholas to try it as soon as possible. Even if it cut down just one infusion per month, I thought it would be a big step forward for us: just one less needle stick would be worth it. Complicating the conversation a bit is the fact that Nicholas is older and his medical care is no longer completely my decision. While he’s not quite ready to make all of his own medical decisions, he is old enough to have a say.

After our most recent HTC visit, he asked about the longer-lasting factor: “why am I not doing that?” We talked about both the factor products that are available and some of the considerations that would go into making the decision to switch. His answer? He’d think about it.

I admit, it can be overwhelming to think about these topics and engage in conversations with my son. I feel fortunate to have not only a wonderful HTC, but also HFA as a great source of information and support.

As overwhelming as it may be with so much change in our community, it is an exciting time. Just look at the comprehensive list of products on the market (p. 9) and the growing list of new and emerging therapies being produced and studied (p. 17)! What a time to be involved in this special community! To our knowledge, this issue offers the first time such a detailed list of products and therapies has been published and I’m thrilled to be able to share it with you all. Our team at HFA worked diligently with manufacturers to ensure that the information in this issue is as timely and accurate as possible.

Also in this issue are a number of informational resources and educational tools to help us all better understand some of the more complex issues we encounter in the community. From a deep dive into how clinical trials work (p. 22), to the infographic of how a drug is brought to market by the FDA (p. 30), this issue is packed with great information. I couldn’t put the issue down until I read it from cover to cover, and hope you enjoy it as much as I did!

Warm regards,

Tracy Cleghorn
Board Chair
There are many ways you can make a contribution to Hemophilia Federation of America as the end of year approaches. Donations are tax-deductible and support the organization's efforts to advocate for the bleeding disorders community.

**Annual Giving | November 28-January 31, 2018**
- Donate online at [www.hemophiliafed.org](http://www.hemophiliafed.org) or send a check to HFA at 820 First Street NE, Suite 720, Washington, DC 20002.
- All donations will support Helping Hands, HFA's financial assistance program.
- Be sure to ask your employer if they match employees’ charitable gifts: a great way to double your gift!

**Cyber Monday | November 27**
- Participate in one of the biggest online shopping days of the year, and support HFA by making your purchases using Amazon Smile.
- When you shop on Amazon Smile, you’ll find the same low prices and vast selection as on Amazon, with the added bonus that Amazon will donate a portion of the purchase price to HFA.
- All it takes is three easy steps:
  - Sign up for Amazon Smile through your Amazon account at [smile.amazon.com](http://smile.amazon.com).
  - Designate Hemophilia Federation of America as your charity of choice.
  - Make holiday purchases on Amazon Smile and a percentage automatically goes to HFA.
- Amazon Smile is available year-round so be sure to designate HFA as your charity of choice today.

**Giving Tuesday | November 28**
- Take part in this annual, international day of giving as the holiday season kicks off and show your support for HFA.
- Donate online at [www.hemophiliafed.org](http://www.hemophiliafed.org) and receive special acknowledgment of your gift.
- Share your giving spirit on social media and encourage others to give by using #givingtuesday.

**Annual Membership**
- Renew or initiate an individual, professional, or corporate membership.
- Individual memberships start at $35 and include a membership-exclusive t-shirt.
- Visit [www.hemophiliafed.org](http://www.hemophiliafed.org) today.

**Other ways to give:**
- When making holiday gift purchases, ask if the store will donate a portion of the sale to a charity.
- In lieu of giving a physical present, consider making a Tribute Gift in the name of a loved one.
- Ask your employer if they match employee charitable gifts

With your help, HFA will be able to deliver educational programming, help families experiencing a financial crisis, advocate for the bleeding disorders community, and so much more. Thank you in advance for your generosity and support.
For most of the 20th century, people living with hemophilia struggled with health problems. Up until the late 1960s, treatment was limited to whole-blood transfusions and icing joints, a procedure that required days in the hospital to recover from a bleed. After cryoprecipitate, a faster, more effective treatment for bleeding episodes, was developed in 1964 by Dr. Judith Graham Pool, life expectancy rose to just over 39 years, a vast improvement from the 27-year median life expectancy during the decades that preceded.

The success with treatment brought new challenges that few in the community could have envisioned. As life expectancy grew, it brought with it new side effects, questions, and concerns for psychiatrists, social workers, and community members as they dealt with the social complications that go along with having a crippling illness. Suicide was, in fact, the most common cause of death among adolescents who suffered from hemophilia.

It’s hard for those who didn’t live through the ‘60s to imagine the impact that the first clotting factor product had on the community when it was administered to a hemophilia patient for the first time in 1967. By early 1968, factor concentrate had entered trials for home treatment and the community began to experience a paradigm shift, suddenly filled with hope that children living with hemophilia would be able to live fuller, healthier, and considerably longer lives.

The Hemophilia Act of 1973 allowed the establishment of federally-funded comprehensive Hemophilia Treatment Centers (HTCs). Today, there are more than 140 HTCs and programs across the country. This, along with a growing national focus on people living with hemophilia, led to a sharp increase in positive outcomes for hemophilia patients, as life expectancy rose to 60 years old.

“Today, there are more than 140 HTCs and programs across the country.”

Bleeding Disorder Products Released to Market

- Total Number of Products on the Market
- Number of Products Released to Market
At the start of 1980s, eight bleeding disorder products were available on the market, a number that even just 10 years prior was unimaginable to most people. Just as the community was beginning to see tangible, positive outcomes from the medical and scientific communities and the increased national dialogue on hemophilia, progress came to an abrupt halt. It was 1982 when the Centers for Disease Control and Prevention (CDC) reported the first cases of pneumocystis carinii pneumonia (an early indicator of the infection later to be known as HIV), among people with hemophilia, contracted through tainted factor products made from infected plasma donors. Many in the hemophilia community became isolated because of discrimination against those with HIV/AIDS, and the fear of being identified as HIV positive. Children, most notably Ryan White and the Ray brothers, were denied entry to school, making national headlines. By the late 1980s, more than half of the hemophilia community had been infected with HIV/AIDS and/or hepatitis C. In those with severe hemophilia, the infection rate was more than 90%.
What followed was a period of action in the hemophilia community throughout the 1990s. National grassroots associations like the Hemophilia-HIV Peer Association, Committee of Ten Thousand (COTT), and Hemophilia Federation of America (HFA) formed to address the heretofore-unheard needs of the community. Meanwhile, National Hemophilia Foundation (NHF) took responsibility for their role in the failure of the public health system to protect the hemophilia community, and joined these grassroots efforts. The gay community became a strong ally, supporting those with hemophilia and HIV/AIDS. After the 1995 release of the Institute of Medicine’s report, “HIV and the Blood Supply,” a legislative effort gained traction, culminating in the passage of the Ricky Ray Hemophilia Relief Fund Act of 1998.

As this community-based activism was taking place, the pharmaceutical industry had 11 new products approved by the FDA between 1990 and 1999. A total of 25 products were approved and available at the close of the 20th century, a vast difference from when the first clotting factor was released in the ’60s. With medical and scientific advancements, the introduction of HTCs, grassroots advocacy organizations, and federal legislation, the hemophilia community could be proud of all it had achieved.

In the last 17 years, the number of products on the market nearly doubled, with 48 products currently on the market treating hemophilia, von Willebrand Disease, rare bleeding disorders, and inhibitors. Since 2010 alone, the community has seen a total of 18 new products released to the market from nine different manufacturers. Three manufacturers—CSL Behring, Novo Nordisk, and Shire—were responsible for more than half of the products that received FDA approval during this time.

The influx of products on the market came with the introduction of new manufacturers to the market as well as a number of mergers, spinoffs, and acquisitions. Just when the community was remembering which products Baxter produced, the name changed to Baxalta which was then quickly followed by a merger with Shire. Biogen produced a spin-off now known as Bioverativ, and Emergent BioSolutions completed a spin-off called Aptevo Therapeutics.

New companies began to enter the market and names like Alnylam, Genentech, Spark Therapeutics, uniQure, among others, began to appear at conferences and in various community news outlets. Almost 30 new and emerging therapies are currently being studied by a number of companies who are looking at treating hemophilia and other bleeding disorders in a number of new ways.

While we can’t know for sure what the future has in store for the community, it’s fair to say that the next few decades will be active, medically and scientifically. The number of products available on the market can’t realistically keep growing at this current steep rate forever, but, at the moment at least, there are no signs of it slowing down anytime soon.

**BE INFORMED:** It’s good to know the origins of the company that provides your factor. Some companies have merged, been acquired, spun-off since 1990, or changed their names along the way.

<table>
<thead>
<tr>
<th>Emergent BioSolutions</th>
<th>Aptevo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyland</td>
<td>Baxter</td>
</tr>
<tr>
<td>Cutter</td>
<td>Miles Laboratories</td>
</tr>
<tr>
<td>Biogen</td>
<td>Bioverativ</td>
</tr>
<tr>
<td>Armour Pharmaceutical</td>
<td>Centeon</td>
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<tr>
<td>Alpha</td>
<td>Grifols</td>
</tr>
<tr>
<td>Bayer (Plasma Div: Product-Koate)</td>
<td>Talecris</td>
</tr>
<tr>
<td>Genetics Institute</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>
Current Products on the Market

With 48 products approved by the Food and Drug Administration (FDA) and available on the market, people living with a bleeding disorder have access to more treatments than ever before. Sifting through the many information sources to learn about these products can be a challenge for any patient or caregiver no matter their comfort level navigating the industry. To help with this process, we’ve compiled a comprehensive list of all bleeding disorder therapies on the market.

This list displays the following information for each product:

- **Manufacturer** – Company that produces and sells the therapy.
- **Product** – Name used to market and sell the therapy.
- **Type** – Indicated method used to create product (Plasma-derived, made from human blood, or recombinant factor concentrates, made from other sources).
- **Half Life** – Amount of time a product stays intact in the bloodstream until its efficacy is halved.
- **Indications** – Bleeding disorder type/factor deficiency the therapy is intended to treat.

We’ve made every effort to ensure the accuracy of the information in this list by using information directly from manufacturers and accessing publicly-available information from websites, like the FDA’s. HFA does not encourage community members to use one product over another, and strongly urges you discuss your treatment options with qualified medical professionals.

The content in this issue is current as of its publishing date, November 2017. Given the fast-paced environment that manufactures and governmental agencies work within, some information could have changed since going to print. Please refer to manufacturers’ or the FDA’s websites for the most up-to-date information.

No information in this issue of Dateline should be interpreted as medical advice. HFA encourages frequent dialogue with experienced healthcare professionals regarding your health and the therapies used to treat your bleeding disorder.
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>Kogenate FS</td>
<td>Recombinant Clotting Factor</td>
<td>13 hours</td>
<td>1993</td>
</tr>
<tr>
<td>Bayer</td>
<td>Kovaltry</td>
<td>Recombinant Clotting Factor</td>
<td>0 to &lt;6 yrs: 12 hours &lt;br&gt;6 to &lt;12 yrs: 12 hours &lt;br&gt;12 to 17 yrs: 14 hours &lt;br&gt;≥18 yrs: 14 hours</td>
<td>2016</td>
</tr>
<tr>
<td>Bioverativ</td>
<td>Eloctate</td>
<td>Recombinant Clotting Factor</td>
<td>19.7 hours (17.4, 22.0) in adults &lt;br&gt;Pediatric: 12 to 17 years: 16.4 hours (14.1, 18.6) &lt;br&gt;6 to 11 years: 14.9 hours (12.0, 17.8) &lt;br&gt;1 to 5 years: 12.7 hours (11.2, 14.1)</td>
<td>2014</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Helixate FS*</td>
<td>Recombinant Clotting Factor</td>
<td>Adults: 13.7-14.8 hours (mean) &lt;br&gt;Children: 10.7 hours (mean)</td>
<td>1993</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Afstyla</td>
<td>Recombinant Clotting Factor</td>
<td>After single dose of 50 IU/kg: &lt;br&gt;Adults (≥18 years): 14.2 hours (mean); &lt;br&gt;Adolescents (12 to &lt;18 years): 14.3 hours (mean); &lt;br&gt;Children: (0 to &lt;6 yrs): 10.4 hours (mean); &lt;br&gt;(6 to &lt;12 years): 10.2 hours (mean)</td>
<td>2016</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Novoeight</td>
<td>Recombinant Clotting Factor</td>
<td></td>
<td>2013</td>
</tr>
<tr>
<td>Octapharma</td>
<td>Nuwiq</td>
<td>Recombinant Clotting Factor</td>
<td>17.1 +/- 11.2 hrs. (Adults); 13.1 +/- 2.6 hrs. (6 to &lt;12 yrs); 11.9 +/- 5.4 hrs. (≥5 yrs.)</td>
<td>2015</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Xyntha</td>
<td>Recombinant Clotting Factor</td>
<td>11.2 ± 5.0 hours(^a,b)</td>
<td>2008</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Xyntha Solofuse</td>
<td>Recombinant Clotting Factor</td>
<td>11.2 ± 5.0 hours(^a,b)</td>
<td>2008</td>
</tr>
<tr>
<td>Shire</td>
<td>Recombinate</td>
<td>Recombinant Clotting Factor</td>
<td>14.6 hrs</td>
<td>1992</td>
</tr>
<tr>
<td>Shire</td>
<td>Advate</td>
<td>Recombinant Clotting Factor</td>
<td>12.03 hrs</td>
<td>2003</td>
</tr>
<tr>
<td>Shire</td>
<td>Adynovate</td>
<td>Recombinant Clotting Factor</td>
<td>14.69 hours (patients over 18 years old) 1.3-1.5 half-life extension compared to ADVATE</td>
<td>2015</td>
</tr>
<tr>
<td>Indications (FVIII, FIX, vWD, Inh, etc)</td>
<td>Notes</td>
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<tr>
<td>VIII</td>
<td>Product is manufactured by Bayer; Helixate is sold and marketed by CSL Behring.</td>
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<td>VIII</td>
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<td>VIII</td>
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<tr>
<td>VIII</td>
<td>Helixate FS will no longer be manufactured after December 2017. Supply will continue to be available through early 2019.</td>
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<td>VIII</td>
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<td>VIII</td>
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<tr>
<td>Indicated in adults and children with Hemophilia A for: 1) On-demand treatment and control of bleeding episodes 2) Perioperative (surgical) management of bleeding and 3) Routine prophylaxis to reduce the frequency of bleeding episodes. NUWIQ is not indicated for the treatment of von Willebrand Disease.</td>
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<tr>
<td>VIII</td>
<td>a-Results from 30 previously treated patients (PTPs) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA. b-Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children.</td>
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<td>VIII</td>
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<td>VIII</td>
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</tbody>
</table>
# VIII Plasma-derived Clotting Factor

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>Monoclate-P</td>
<td>Plasma-derived Clotting Factor</td>
<td>17.5 hours (mean)</td>
<td>1972</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Humate-P</td>
<td>Plasma-derived Clotting Factor</td>
<td>12.2 hours (mean) in Hemophilia A</td>
<td>1986</td>
</tr>
<tr>
<td>Grifols</td>
<td>Alphanate</td>
<td>Plasma-derived Clotting Factor</td>
<td></td>
<td>1978</td>
</tr>
<tr>
<td>Kedrion BioPharma</td>
<td>Koate-DVI</td>
<td>Plasma-derived Clotting Factor</td>
<td></td>
<td>1974</td>
</tr>
<tr>
<td>Shire</td>
<td>Hemofil M NH</td>
<td>Plasma-derived Clotting Factor</td>
<td>14.8 hrs</td>
<td>1966</td>
</tr>
</tbody>
</table>

# VIII Other Products

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>Stimate (Desmopressin Nasal Spray)</td>
<td>Nasal Spray</td>
<td>Adults: 13.7-14.6 hours (mean)</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Children: 10.7 hours (mean)</td>
<td></td>
</tr>
<tr>
<td>Pfizer</td>
<td>Cyklokapron (tranexamic acid injection)</td>
<td>Antifibrinolytic Agent</td>
<td>2 hours†</td>
<td>1986</td>
</tr>
<tr>
<td>Ferring</td>
<td>DDAVP (Desmopressin)</td>
<td>Intravenous Injection-Factor catalyst/factor booster/factor precipitator</td>
<td></td>
<td>1978</td>
</tr>
<tr>
<td>Indications (FVIII, FIX, vWD, Inh, etc)</td>
<td>Notes</td>
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<td></td>
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</tr>
<tr>
<td>VIII</td>
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<tr>
<td>VIII, vWD</td>
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</tr>
<tr>
<td>VIII, vWD with exceptions</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
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<tr>
<td>VIII</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
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<tr>
<td>VIII</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications (FVIII, FIX, vWD, Inh, etc)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIII greater than 5%; mild to moderate vWD type I with factor VIII levels greater than 5%</td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td>f-terminal elimination phase</td>
</tr>
<tr>
<td>VIII greater than 5%; mild to moderate vWD type I with factor VIII levels greater than 5%</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
</tr>
</tbody>
</table>
### IX Recombinant Clotting Factor

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptevo Therapeutics</td>
<td>IXINITY</td>
<td>Recombinant Clotting Factor</td>
<td>24 hours</td>
<td>2015</td>
</tr>
<tr>
<td>Bioverativ</td>
<td>Alprolix</td>
<td>Recombinant Clotting Factor</td>
<td>86.52 Hrs (37.2%) in adults</td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric: 12 to 17 years: 83.59 Hrs (19.1%)</td>
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<tr>
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<td>6 to 11 years: 72.23 Hrs (23.1%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 to 5 years: 65.40 Hrs (32.1%)</td>
<td></td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Idelvion</td>
<td>Recombinant Clotting Factor</td>
<td>After single dose of 50 IU/kg: Adults: 104 hours; Pediatric: 11 to 17 years: 83.59 Hrs (19.1%)</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adolescents (12 to &lt;18 years): 89 hours (mean); Children: (0 to 6 years): 90 hours (mean); and (6 to &lt;12 years): 93 hours (mean)</td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>REBINYN</td>
<td>Recombinant Clotting Factor</td>
<td></td>
<td>2017</td>
</tr>
<tr>
<td>Pfizer</td>
<td>BeneFIX</td>
<td>Recombinant Clotting Factor</td>
<td>18.8 ± 5.4 hours (range 11 to 36 hours)(\text{f,e})</td>
<td>1997</td>
</tr>
<tr>
<td>Shire</td>
<td>Rixibius</td>
<td>Recombinant Clotting Factor</td>
<td>25.7 (adults over 12 years old)</td>
<td>2013</td>
</tr>
</tbody>
</table>

### IX Plasma-derived Clotting Factor

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>Mononine</td>
<td>Plasma-Derived Clotting Factor</td>
<td>22.6 to 25.3 hours (mean)</td>
<td>1992</td>
</tr>
<tr>
<td>Grifols</td>
<td>Alphanine SD</td>
<td>Plasma-Derived Clotting Factor</td>
<td></td>
<td>1990</td>
</tr>
<tr>
<td>Grifols</td>
<td>Prohlinine SD</td>
<td>Plasma-Derived Clotting Factor</td>
<td></td>
<td>1990</td>
</tr>
<tr>
<td>Shire</td>
<td>Bebulin VH</td>
<td>Plasma-Derived Clotting Factor</td>
<td>19.97 hrs (Three half-lives are reported in the label and this is the middle value)</td>
<td>1970</td>
</tr>
</tbody>
</table>

### IX Other Products

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Cyklokapron (tranexamic acid injection)</td>
<td>Antifibrinolytic Agent</td>
<td>2 hours(\text{f})</td>
<td>1986</td>
</tr>
</tbody>
</table>

### Inhibitor Products

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech</td>
<td>HEMLIBRA</td>
<td>Therapeutic Bi-specific Antibody</td>
<td>-4 weeks</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>NovoSeven RT</td>
<td>Recombinant Clotting Factor</td>
<td></td>
</tr>
<tr>
<td>Shire</td>
<td>FEIBA NF</td>
<td>Plasma-Derived Clotting Factor</td>
<td>FII half-life = 72 hours, sustained activity (thrombin generation returns to baseline after 8-12 hours) and long dosing interval (8-12 hours)</td>
</tr>
<tr>
<td>Indications (FVIII, FIX, vWD, Inh, etc)</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicated for control and prevention of bleeding episodes and for perioperative management. Not indicated for induction of immune tolerance in patients with Hemophilia B.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FDA Approved

<table>
<thead>
<tr>
<th>Year</th>
<th>Indications (FVIII, FIX, vWD, Inh, etc)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>VIII with inhibitor; IX with inhibitor; VII deficiency, Glanzmann’s, acquired hemophilia thrombasthenia</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>VIII with inhibitor, IX with inhibitor</td>
<td></td>
</tr>
</tbody>
</table>
## vWD Products

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>Humate-P</td>
<td>Plasma-Derived Clotting Factor</td>
<td>10-11 hours (median) for vWD</td>
</tr>
<tr>
<td>Ferring Pharmaceuticals</td>
<td>DDAVP (Desmopressin)</td>
<td>Intravenous Injection-Factor catalyst/factor booster/factor precipitator</td>
<td></td>
</tr>
<tr>
<td>Grifols</td>
<td>Alphanate</td>
<td>Plasma-Derived Clotting Factor</td>
<td></td>
</tr>
<tr>
<td>Octapharma</td>
<td>Wilate</td>
<td>Plasma-Derived Clotting Factor</td>
<td>VWF: 15.8 hours; FVIII: 19.6 hours</td>
</tr>
<tr>
<td>Shire</td>
<td>Vonvendi</td>
<td>Recombinant Clotting Factor</td>
<td>For 50IU/kg mean (SD) 21.9 (8.36)</td>
</tr>
</tbody>
</table>

## Other Rare Bleeding Disorder Products

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Type</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akorn</td>
<td>Amicar (amniocaproic acid - oral solution and tablets)</td>
<td>Oral Solution and Tablets</td>
<td></td>
</tr>
<tr>
<td>Bio Products Laboratory</td>
<td>Coagadex</td>
<td>Plasma-Derived Clotting Factor</td>
<td>“Mean (CVs) = 30.3 hours (22.8)”</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Corifact</td>
<td>Plasma-Derived Clotting Factor</td>
<td>6.6 hours by Berichrom Assay method (mean)</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>RiaSTAP</td>
<td>Plasma-Derived Clotting Factor</td>
<td>78.7 hours (mean)</td>
</tr>
<tr>
<td>Ferring Pharmaceuticals</td>
<td>Lysteda (tranexamic acid tablets)</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Tretten</td>
<td>Recombinant Clotting Factor</td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>NovoSeven RT</td>
<td>Recombinant Clotting Factor</td>
<td></td>
</tr>
<tr>
<td>Octapharma</td>
<td>Fibryna</td>
<td>Plasma-derived Fibrinogen Concentrate</td>
<td>75.9 hours (mean)</td>
</tr>
<tr>
<td>Shire</td>
<td>Obizur</td>
<td>Recombinant Clotting Factor</td>
<td>Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses</td>
</tr>
<tr>
<td>FDA Approved</td>
<td>Indications (FVIII,FIX,vWD, Inh, etc)</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>vWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>VIII greater than 5%; mild to moderate vWD type I with factor VIII levels greater than 5%</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>Surgical and/or invasive procedures in adult and pediatric patients with vWD in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe vWD (type 3) undergoing major surgery.</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Patients with vWD for on-demand treatment and control of bleeding episodes, and for perioperative management of bleeding.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>vWD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**vWD Products**

<table>
<thead>
<tr>
<th>FDA Approved</th>
<th>Indications (FVIII,FIX,vWD, Inh, etc)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>vWD</td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>VIII greater than 5%; mild to moderate vWD type I with factor VIII levels greater than 5%</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
</tr>
<tr>
<td>1978</td>
<td>Surgical and/or invasive procedures in adult and pediatric patients with vWD in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe vWD (type 3) undergoing major surgery.</td>
<td>Didn’t respond to HFA’s request to confirm information. Data pulled from public sources.</td>
</tr>
<tr>
<td>2009</td>
<td>Patients with vWD for on-demand treatment and control of bleeding episodes, and for perioperative management of bleeding.</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>vWD</td>
<td></td>
</tr>
</tbody>
</table>
Navigating Patient Assistance Programs

HFA’s comprehensive list of available programs.

With the uncertainty of healthcare, many in the bleeding disorders community are concerned about the future of cost and access to factor products. Co-payments and out-of-pocket expenses can be devastating on a family’s budget. Assistance programs can provide a source of relief.

The HFA team maintains a comprehensive list of programs that are available to the community and updates it regularly. Visit our site to see which of these programs might apply to you and your family:

- Factor Co-Pay Programs
- Product Assistance Programs
- Hepatitis C Virus Co-Pay & Patient Assistance Programs
- Additional Resources

Visit HFA’s resource library on www.hemophiliafed.org today!
Within the past decade alone, medical research and scientific advancements have reshaped the way the bleeding disorders community looks at treatment. Discussions of a cure, or long-lasting, one-time treatment options, no longer seem so far-fetched, but they are instead very likely outcomes of a scientific breakthrough. Numerous companies and research teams are evaluating their products and therapies through the FDA’s clinical trial process right now. The following list of emerging therapies contains the following information:

- **Manufacturer** – Company that is researching/studying a product/trial.
- **Investigational Therapeutic Product Name** – Product name used during a research/trial. Usually this name is changed when a product is approved and brought to market.
- **Type** – Method used to create the product/therapy.
- **Official Title of Study** – Submitted to FDA for clinical trial usage.
- **Phase** – The current stage in the FDA approval process.
- **Indications** – Bleeding disorder type/factor deficiency the therapy is intended to treat.

For a more detailed overview of how a product is brought to market under FDA’s guidelines, turn to page 30.

The content in this issue is current as of its publishing date, November 2017. Given the fast-paced environment that manufactures and governmental agencies work within, some information could have changed since going to print. Please refer to manufacturers’ or the FDA’s websites for the most up-to-date information.

No information in this issue of Dateline should be interpreted as medical advice. HFA encourages frequent dialogue with experienced healthcare professionals regarding your health and the therapies used to treat your bleeding disorder.
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Investigational Therapeutic Product Name</th>
<th>Type</th>
<th>Official Title of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>BAY94-9027</td>
<td>Biologic, long-acting recombinant VIII molecule</td>
<td>A Phase II/III, Multicenter, Partially Randomized, Open Label Trial Investigating Safety and Efficacy of On-demand and Prophylactic Treatment With BAY94-9027 in Severe Hemophilia A</td>
</tr>
<tr>
<td>Bayer</td>
<td>BAY1093884 (VIII, IX)</td>
<td>Anti-Tissue Factor Pathway Inhibitor Antibody</td>
<td>A Phase 1, First in Man, Multicenter, Open Label, Single Escalating Dose Study of BAY1093884 in Subjects With Severe Hemophilia Types A or B, With or Without Inhibitors</td>
</tr>
<tr>
<td>Catalyst Biosciences</td>
<td>CB 2679d/1SU304</td>
<td>Recombinant IX</td>
<td>A Phase 1, Open-label, Multi-center, Dose-escalation Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of 1SU304 in Previously Treated Hemophilia B Patients</td>
</tr>
<tr>
<td>Catalyst Biosciences</td>
<td>Marzeptacog alfa (activated)</td>
<td>Recombinant VIIa</td>
<td>Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B subjects with an inhibitor</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>Recombinant Coagulation Factor IX Albumin Fusion Protein, rIX-FP</td>
<td>Recombinant IX</td>
<td>A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects With Hemophilia B</td>
</tr>
<tr>
<td>CSL Behring</td>
<td>rVIIa-FP (CSL689) Eptacog alfa (activated)</td>
<td>Recombinant VIIa</td>
<td>A Multicenter, Open-label, Multiple-dose, Dose Escalation Study to Investigate the Pharmacokinetics, Efficacy, and Safety of rVIIa-FP (CSL 689) in Subjects With Hemophilia (A or B) and Inhibitors</td>
</tr>
<tr>
<td>LFB SA (HEMA Biologics)</td>
<td>Coagulation FVIIa (Recombinant) Eptacog Beta or LR789</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>PERSEPT 1: A Phase III Study on the Safety, Pharmacokinetics and Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients With Inhibitors to Factor VIII or IX</td>
</tr>
<tr>
<td>LFB SA (HEMA Biologics)</td>
<td>Coagulation FVIIa (Recombinant) Eptacog Beta or LR789</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>PERSEPT 2: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to &lt;12 years old with Inhibitors to Factor VIII or IX</td>
</tr>
<tr>
<td>LFB SA (HEMA Biologics)</td>
<td>Coagulation FVIIa (Recombinant) Eptacog Beta or LR789</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>PERSEPT 3: A Phase III Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients With Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)</td>
</tr>
<tr>
<td>LFB SA (HEMA Biologics)</td>
<td>high purity VWF concentrate</td>
<td>High purity VWF concentrate</td>
<td>Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients</td>
</tr>
<tr>
<td>LFB SA (HEMA Biologics)</td>
<td>high purity VWF concentrate</td>
<td>High purity VWF concentrate</td>
<td>Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus-inactivation/removal methods</td>
</tr>
<tr>
<td>Opko Biologics</td>
<td>MOD-5014</td>
<td>Long-acting Recombinant VIIa</td>
<td>A Phase 1/2a, Open-Label, Multicenter, Dose Escalation Study to Assess the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) Profile of a Long Acting Recombinant FVIIa (MOD-5014) in Adult Men With Hemophilia A or B</td>
</tr>
<tr>
<td>Opko Biologics</td>
<td>MOD-5014</td>
<td>Long-acting Recombinant VIIa</td>
<td>A Phase 1, Randomized, Single-blind, Placebo-controlled, Single Dose, Dose-escalated Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Profile of Subcutaneous Administration of a Long-acting Recombinant Factor VIIa in Healthy Adult Males</td>
</tr>
<tr>
<td>Sinocelltech Ltd.</td>
<td>SCT800</td>
<td>Recombinant VIII</td>
<td>A Multi-center, Phase III, Non-controlled, Open-label Trial to Evaluate the Safety and Efficacy of SCT800 for On-demand Treatment in Previously Treated Patients With Hemophilia A</td>
</tr>
<tr>
<td>Phase</td>
<td>Indications (FVIII, FIX, vWD, Inh, etc)</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Phase 2  &lt;br&gt; Phase 3</td>
<td>VIII</td>
<td>BLA accepted, 10/30/17</td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>Severe VIII, Severe IX</td>
<td>FDA Orphan Drug Status granted, 9/26/2017</td>
<td></td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>IX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>VII or IX with inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Severe IX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVIII with inhibitors: Phase 2  &lt;br&gt; FIX: Phase 3</td>
<td>VIII, IX with inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Congenital VIII or IX with inhibitors: &gt;12 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Congenital VIII or IX with inhibitors: birth to &lt;12 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Congenital VIII or IX with inhibitors: Prevention of excessive bleeding for elective surgery or other invasive procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult and pediatric patients with severe vWD and patients with mild or moderate vWD where desmopressin treatment alone is known or suspected to be ineffective or contraindicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult and pediatric patients with severe vWD and patients with mild or moderate vWD where desmopressin treatment alone is known or suspected to be ineffective or contraindicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1  &lt;br&gt; Phase 2</td>
<td>Moderate to Severe VIII or IX with or without inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>VIII, IX with inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Moderate to Severe IX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Novel Therapies

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Investigational Therapeutic Product Name</th>
<th>Type</th>
<th>Official Title of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alnylam</td>
<td>fitusiran ALN-AT3SC</td>
<td>RNAi</td>
<td>A Phase I Single-ascending and Multiple-ascending Dose, Safety, Tolerability and Pharmacokinetics Study of Subcutaneously Administered ALN-AT3SC in Healthy Adult Volunteers and Hemophilia A or B Patients (Moderate or Severe Hemophilia)</td>
</tr>
<tr>
<td>Alnylam</td>
<td>fitusiran ALN-AT3SC</td>
<td>RNAi</td>
<td>An Open-label Extension Study of Subcutaneously Administered ALN-AT3SC in Patients With Moderate or Severe Hemophilia A or B Who Have Participated in a Previous Clinical Study With ALN-AT3SC</td>
</tr>
<tr>
<td>Genentech (Roche)</td>
<td>HEMLIBRA, emicizumab-kxwh, aka ACE910</td>
<td>Bi-specific antibody</td>
<td>A Randomized, Multicenter, Open-label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Patients Without Inhibitors (HAVEN 3)</td>
</tr>
<tr>
<td>Genentech (Roche)</td>
<td>HEMLIBRA, emicizumab-kxwh, aka ACE910</td>
<td>Bi-specific antibody</td>
<td>A Multicenter, Open-Label, Phase III Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks (Q4W) in Patients With Hemophilia A (HAVEN 4)</td>
</tr>
</tbody>
</table>

### Emerging Therapies | Gene Therapy

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Investigational Therapeutic Product Name</th>
<th>Type</th>
<th>Official Title of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioMarin Pharmaceutical</td>
<td>BMN 270, aka Roxaparvovec</td>
<td>Adenovirus-associated virus (AAV) based gene therapy vector</td>
<td>Gene Therapy Study in Severe Haemophilia A Patients</td>
</tr>
<tr>
<td>Sangamo Therapeutics</td>
<td>SB-FIX</td>
<td>Genome Editing</td>
<td>A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy Via Zinc Finger Nuclease (ZFN) Mediated Targeted Integration of SB-FIX in Adult Subjects With Severe Hemophilia B</td>
</tr>
<tr>
<td>Sangamo Therapeutics, in partnership with Pfizer</td>
<td>SB-525</td>
<td>Gene Therapy</td>
<td>A Phase 1/2, Open-Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 (Recombinant AAV2/8 Human Factor 8 Gene Therapy) in Adult Subjects With Severe Hemophilia A</td>
</tr>
<tr>
<td>Shire</td>
<td>SHP654 (aka BAX888)</td>
<td>Gene Therapy</td>
<td>As of publication, trial name has not been announced. Trial expected to begin by the end of 2017.</td>
</tr>
<tr>
<td>St. Jude</td>
<td>scAAV 2/8-LP1-hFIXco</td>
<td>Gene Transfer</td>
<td>An Open Label Dose-Escalation Study Of A Self Complementary Adeno-Associated Viral Vector (scAAV 2/8-LP1-hFIXco) For Gene Transfer in Hemophilia B</td>
</tr>
<tr>
<td>uniQure</td>
<td>AMT-060 (AAV5-hFIX)</td>
<td>Gene Transfer</td>
<td>A Phase 1/II, Open-label, Uncontrolled, Single-dose, Dose-ascending, Multi-centre Trial Investigating an Adeno-associated Viral Vector Containing a Codon-optimized Human Factor IX Gene (AAV5-hFIX) Administered to Adult Patients With Severe or Moderately Severe Hemophilia B</td>
</tr>
</tbody>
</table>
# Novel Therapies

<table>
<thead>
<tr>
<th>Phase</th>
<th>Indications (FVIII, FIX, vWD, Inh, etc)</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 - Suspended 9/7/2017 with plans to reinitiate by year-end.</td>
<td>VIII, IX, VIII with inhibitors, IX with inhibitors</td>
<td></td>
</tr>
<tr>
<td>Phase 1 Phase 2 - suspended 9/7/2017</td>
<td>VIII, IX, VIII with inhibitors, IX with inhibitors</td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Severe VIII</td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Severe VIII and VIII with inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Indications (FVIII, FIX, vWD, Inh, etc)</th>
<th>FDA Status</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Phase 2</td>
<td>VIII</td>
<td>Breakthrough designation, 10/27/2017</td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>Severe IX</td>
<td>IND cleared. Orphan drug designation.</td>
<td></td>
</tr>
<tr>
<td>Phase 1 Phase 2</td>
<td>Severe VIII</td>
<td>IND cleared. Orphan drug designation by FDA and EMA. Fast track from FDA.</td>
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<td>VIII</td>
<td>Orphan drug designation; Breakthrough Designation; 7/21/16</td>
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Learn About Clinical Studies
By the US National Library of Medicine

What Is a Clinical Study?
A clinical study involves research using human volunteers (or “participants”) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called “interventional studies”) and observational studies. ClinicalTrials.gov includes both interventional and observational studies.

Clinical Trials
In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants’ behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives, including no intervention at all. The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases.

Clinical trials used in drug development are usually classified by phase. These phases are defined by the Food and Drug Administration (FDA).

Some people who are not eligible to participate in a clinical trial may be able to get experimental drugs or devices outside of a clinical trial through expanded access.

Observational Studies
In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions, which can include medical products such as drugs or devices, or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator as they would be in a clinical trial. For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.

Who Conducts Clinical Studies?
Every clinical study is led by a principal investigator, who is often a medical doctor. Clinical studies also have a research team that may include doctors, nurses, social workers, and other health care professionals.

Clinical studies can be sponsored, or funded, by pharmaceutical companies, academic medical centers, voluntary groups, and other organizations, in addition to Federal agencies such as the National Institutes of Health, the US Department of Defense, and the US Department of Veterans Affairs. Doctors, other health care providers, and other individuals can also sponsor clinical research.

Where are Clinical Studies Conducted?
Clinical studies can take place in many locations, including hospitals, universities, doctors’ offices, and community clinics. The location depends on who is conducting the study.

How Long do Clinical Studies Last?
The length of a clinical study varies, depending on what is being studied. Participants are told how long the study will last before they enroll.

Reasons for Conducting Clinical Studies
In general, clinical studies are designed to add to medical knowledge related to the treatment, diagnosis, and prevention of diseases or conditions. Some common reasons for conducting clinical studies include:

• Evaluating one or more interventions, like drugs, medical devices, approaches to surgery or radiation therapy, for treating a disease, syndrome, or condition
• Finding ways to prevent the initial development or recurrence of a disease or condition. These can include medicines, vaccines, or lifestyle changes, among other approaches.
• Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition
Examinings methods for identifying a condition or the risk factors for that condition

Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness

**Participating in Clinical Studies**

A clinical study is conducted according to a research plan known as the protocol. The protocol is designed to answer specific research questions and safeguard the health of participants. It contains the following information:

- The reason for conducting the study
- The eligibility criteria, or who may participate in the study
- The number of participants needed
- The schedule of tests, procedures, or drugs and their dosages
- The length of the study
- What information will be gathered about the participants

**Who Can Participate in a Clinical Study?**

Clinical studies have standards outlining who can participate. These standards are called eligibility criteria and are listed in the protocol. Some research studies seek participants who have the illnesses or conditions that will be studied, other studies are looking for healthy participants, and some studies are limited to a predetermined group of people who are asked by researchers to enroll.

**Eligibility**

The factors that allow someone to participate in a clinical study are called inclusion criteria, and the factors that disqualify someone from participating are called exclusion criteria. They are based on characteristics such as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

**How are Participants Protected?**

Informed consent is a process used by researchers to provide potential and enrolled participants with information about a clinical study. This information helps people decide whether they want to enroll or continue to participate in the study. The informed consent process is intended to protect participants and should provide enough information for a person to understand the risks of, potential benefits of, and alternatives to, the study. In addition to the informed consent document, the process may involve recruitment materials, verbal instructions, question-and-answer sessions, and activities to measure participant understanding. In general, a person must sign an informed consent document before joining a study to show that he or she was given information on the risks, potential benefits, and alternatives to the study. Signing the document and providing consent is not a contract. Participants may withdraw from a study at any time, even if the study is not over. See the Questions to Ask section of this article for questions to ask a health care provider or researcher about participating in a clinical study.

**Institutional Review Boards**

Each federally-supported or conducted clinical study and each study of a drug, biological product, or medical device regulated by FDA must be reviewed, approved, and monitored by an institutional review board (IRB). An IRB is made up of doctors, researchers, and members of the community. Its role is to make sure that the study is ethical and that the rights and welfare of participants are protected. This includes making sure that research risks are minimized and are reasonable in relation to any

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**The Five Phases of a Clinical Trial:**

**EARLY PHASE 1 (Formerly listed as “Phase 0”):** Exploratory study involving very limited human exposure to the drug, with no therapeutic or diagnostic goals. Examples would include screening studies and microdose studies.

**PHASE 1:** Studies that are usually conducted with healthy volunteers and that emphasize safety. The goal is to find out what the drug’s most frequent and serious adverse events are and, often, how the drug is metabolized and excreted.

**PHASE 2:** Studies that gather preliminary data on effectiveness, as in whether the drug works in people who have a certain disease or condition. For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance, called a placebo, or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.

**PHASE 3:** Studies that gather more information about safety and effectiveness by studying different populations and different dosages, and by using the drug in combination with other drugs.

**PHASE 4:** Studies occurring after FDA has approved a drug for marketing. These include post-market requirement and commitment studies that are required of or agreed to by the study sponsor. These studies gather additional information about a drug’s safety, efficacy, or optimal use.
potential benefits, among other responsibilities. The IRB also reviews the informed consent document.

In addition to being monitored by an IRB, some clinical studies are also scrutinized by data monitoring committees, also known as “Data and Safety Monitoring Boards”.

Various Federal agencies, including the Office of Human Subjects Research Protection and FDA, have the authority to determine whether sponsors of certain clinical studies are adequately protecting research participants.

**Relationship to Usual Health Care**

Typically, participants continue to see their usual health care providers while enrolled in a clinical study. While most clinical studies provide participants with medical products or interventions related to the illness or condition being studied, they do not provide extended or complete health care. By having his or her usual health care provider work with the research team, a participant can make sure that the study protocol will not conflict with other medications or treatments that he or she receives.

**Considerations for Participation**

Participating in a clinical study contributes to medical knowledge. The results of these studies can make a difference in the care of future patients by providing information about the benefits and risks of therapeutic, preventative, or diagnostic products or interventions.

Clinical trials provide the basis for the development and marketing of new drugs, biological products, and medical devices. Sometimes, the safety and the effectiveness of the experimental approach or use may not be fully known at the time of the trial. Some trials may provide participants with the prospect of receiving direct medical benefits, while others do not. Most trials involve some risk of harm or injury to the participant, although it may not be greater than the risks related to routine medical care or disease progression. For trials approved by IRBs, the IRB has decided that the risks of participation have been minimized and are reasonable in relation to anticipated benefits. Many trials require participants to undergo additional procedures, tests, and assessments based on the study protocol. These requirements will be described in the informed consent document. A potential participant should also discuss these issues with members of the research team and with his or her usual health care provider.

**Questions to Ask**

Anyone interested in participating in a clinical study should know as much as possible about the study and feel comfortable asking the research team questions about the study, the related procedures, and any expenses. The following questions may be helpful during such a discussion. Answers to some of these questions are provided in the informed consent document. Many of the questions are specific to clinical trials, but some also apply to observational studies.
If you have a bleeding disorder, chances are you’re no stranger to engaging in conversations about your health with medical, research, and pharmaceutical staff. Emergency rooms, doctors’ offices, pharmaceutical company offices, conference rooms, and exhibit halls have all become places where you might engage in medical discussions. Each of these venues has different, but similar, codes of ethics to follow when engaging in conversations about your health, but all require obtaining your informed consent before conducting healthcare intervention or research through a study or trial.

Consent can only be obtained from a mentally competent adult or a legally authorized representative of a mentally incompetent adult. This legal status refers to the capacity of a person to act on their own behalf and their ability to understand the information presented, to appreciate the consequences of acting or not acting on that information, and to make a choice. A parent or legal guardian provides consent for a minor. However, children 12 and older who are asked to participate in a research project must do so voluntarily and must verbally assent to the research project. The explanation of the project and the language used must be appropriate to the child. In some localities, even children as young as seven years old are asked to assent to participate in research studies. The local Institutional Review Board (IRB) that approves the study can provide you with more information about consent as it relates to children.

Under US Food and Drug Administration (FDA) regulations, an IRB is an administrative body that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications needed to secure approval, or disapprove, research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

Consent works differently in a hospital setting versus a research/clinical trial setting. In the research/clinical trial setting, the first step to understanding it is actually discovering that a research study or clinical trial exists. You may learn about the existence of a research project or clinical trial via mail, telephone, through a friend, or during an in-person visit to your doctor. You also may learn about an opportunity to participate in a research project or clinical trial at an exhibit hall during a conference. No matter how you hear about a research project or clinical trial, it is important to learn as much as you can before you choose to participate. After you become aware
of a research project, the researcher inviting you to participate in the research or clinical trial must tell you how the project works, how it is structured, outcomes and research methods. If the person inviting you to participate is not able to answer all your questions, they must provide you with the name and contact information of someone who can. It is important to have all your questions answered to your satisfaction before you agree to participate in a research study or clinical trial.

Each time you agree to participate in a research study or clinical trial, the researcher must have your consent to participate. The document explaining the details of the research project or clinical trial is the consent form. The consent form has many elements, but the purpose of the document is to make sure you understand everything about the research project or clinical trial. It is important to read and understand every aspect of the consent form before you sign it.

Your signature on the form indicates that you understand the risks and benefits of participating and that you agree to participate. If you sign a consent form, you should also receive a copy of it. The form you sign and the copy you receive should be identical. Save your consent form in a safe place for future reference: you’ll need it in case you want to withdraw your consent at some time in the future.

If the research focus changes after you agree to participate (for example, the researcher decides to use your blood samples for a new clinical trial at a different company), the researcher must secure your permission again. Any time the research focus changes, the researcher must get your permission unless it was specified in the consent form that your permission would not be needed if there were a change in the research focus.

Sometimes, individuals who are participating in a study or clinical trial wish to withdraw their informed consent, and that’s okay. If you change your mind and decide to withdraw consent from a research study or clinical trial, contact the Principal Investigator, the person in charge of the research project. Every consent form should have, at a minimum, the Principal Investigator’s name, address, and phone number listed for reference. Also, unless otherwise specified, it is possible that the information or data you provide – prior to withdrawing from a research project or clinical trial – may still be used. So, before you agree to participate in a research project or clinical trial, find out if your information and/or data will be used regardless of whether you later decide to withdraw consent.

The informed consent process involves information being shared between a patient or research participant and the doctor or researcher. The patient or research participant has a right to be informed, but they also have a responsibility to ask questions. The doctor or researcher has the responsibility to conduct ethical care or research and the responsibility to be honest about all aspects of the medical or research process. Here are some of the different responsibilities that the various parties assume:

**Patient and Participant Rights and Responsibilities**
- Understand that should have your questions answered to your satisfaction before you agree to treatment or to participate as a research participant.
- Understand the purpose of the treatment/research, before you agree to participate.
- Understand you can refuse treatment and you can refuse to participate in the research project.
- Understand if you can stop treatment or withdraw from the research project after it has started.
- Know that you have a right to privacy.

**Doctor and Researcher Responsibilities**
- Discuss the purpose of the treatment or research with the potential research subject.
- Provide patient/research participant with enough time to consider whether he/she wants to take part in the treatment or join the research project.
- Do not force or unduly influence a patient/participant into taking part in a treatment or join a research project.
- Discuss the risks and benefits of participating in the treatment or research.
- Respect the privacy of the patient/research participant.
- Adhere to and honor the ethical guidelines established by the National Institutes of Health (NIH) for human subject research when conducting studies.

**More than a signature:**
**INFORMED CONSENT IS ABOUT YOUR UNDERSTANDING AND WILLINGNESS to participate in a study, NOT ABOUT SIGNING A FORM.**
Tips for Understanding Clinical Trials & Research Studies

We cannot emphasize enough that participants, sometimes referred to as Human Subjects in a clinical research setting, should ask questions about their participation in a clinical trial or research study prior to signing up. Here are questions you should ask about a clinical trial or research study and the information you should glean from asking.

What should I ask?

• Is a written copy of the research procedures available?
• What are the benefits and risks of this research project?
• How will I be informed if there are changes to this project?
• Am I waiving any of my rights by signing this consent form?
• May I ask a person I trust to read this document?
• Will my name and address be kept confidential or will it be shared with others?
• How will my information be stored to protect my privacy?
• May I refuse to participate in this research project?
• What if I change my mind after I agree to participate?
• How do I withdraw my consent after I sign the form?
• If I withdraw my consent and stop participating, what will happen with the information already collected from me?
• Are there negative consequences if I withdraw my consent?
• (In case of pharmaceutical trials) Will I be given the actual medication or a placebo?
• (If English is not your first language) Is the information available in my preferred language?

What have I learned?

• The purpose of the research.
• The name, address and phone number of the Principal Investigator.
• How long I am expected to participate.
• If any of the medications or procedures is experimental.
• The possible risks or discomforts.
• If there are any alternative procedures or courses of treatment.
• If my information and medical records will be kept confidential.
• If I will be paid for my participation.
• The medical treatments available if I get injured.
• Who I can call if I have questions.
• If I am required to participate in this study.
• If there is a penalty if I refuse to participate.
• If there is a penalty if I stop participating at any time.
Recent advances in hemophilia treatment have moved beyond standard factor replacement and even beyond by-passing strategies such as recombinant factor VIIa or FEIBA. Scientists are investigating creative new ways to manipulate the coagulation cascade to provide hemostasis for patients with bleeding disorders, and gene therapy is more promising than ever. This is particularly exciting for those patients with inhibitors. This short, technical review will attempt to summarize some of these products.

**Factor VIII Mimetic**

Emicizumab (Genentech), previously known as ACE910, is a humanized bispecific antibody which can take the place of factor VIII (FVIII) in coagulation by bridging between activated factors IX and X. Studies have recently been published showing good results with the weekly use of Emicizumab, dosed subcutaneously, in hemophilia A patients. Abstracts presented at the International Society on Thrombosis and Haemostasis Congress in Berlin this July suggested factor IX-deficient patients with a minimal plasma factor IX (FIX) level and patients with Type 2N von Willebrand Disease may also benefit from this drug, though the exact mechanism is not understood. There have been three cases of thrombotic microangiopathy, a serious hematologic disorder, and two thrombotic (clotting) events reported in patients who were receiving Emicizumab prophylaxis, when Emicizumab was utilized along with repeated high doses of a bypassing agent for over 24 hours, to treat breakthrough bleeds. Caution should be exercised when using any bypassing agent with this medication for that reason. Additionally, presence of Emicizumab affects the FVIII activity and inhibitor assays employed in most laboratories.

**RNA Interference Targeting Antithrombin**

The investigational drug Fitusiran (Alnylam) utilizes RNA interference (RNAi) of antithrombin to restore balance to the clotting system and decrease bleeding in patients with hemophilia. The RNAi decreases the production of antithrombin to improve thrombin generation by “taking the brakes off.” Fitusiran can be used in either Hemophilia A or B, with and without inhibitors, and may be useful in other bleeding disorders, though this has not yet been studied. Clinical trial data suggest that monthly subcutaneous dosing of Fitusiran is effective for hemostasis. On September 7, 2017, Alnylam reported a fatal thrombotic event in a patient with hemophilia A without inhibitors in the Phase 2 open-label extension (OLE) study of Fitusiran. As a result, Alnylam has suspended dosing in all ongoing Fitusiran studies pending further review of the safety event. Alnylam aims to resume dosing as soon as possible upon agreement with global regulatory authorities and with appropriate protocol amendments in place for enhanced patient safety monitoring.

**Blockade of Tissue Factor Pathway Inhibitor**

Concizumab (Novo Nordisk) is a monoclonal antibody directed against tissue factor pathway inhibitor (TFPI). A Phase 1b trial in hemophilia A patients has recently been completed. Phase 2 studies have been initiated. Like the other drugs previously dis-
Cussed, Concizumab is administered subcutaneously. Similar to Fitusiran, the concept of TFPI inhibition is to reduce or block a naturally occurring inhibitor of coagulation and restore balance to the clotting system, thus enhancing thrombin generation.

**Gene Therapy**

Gene therapy is an experimental technique which aims to treat a genetic disorder by inserting a gene into a patient’s cells to replace an abnormal gene, instead of using drugs, like factor replacement, as treatment. In gene therapy research for hemophilia, a working copy of the factor VIII or factor IX gene is “packaged” inside a viral vector (or transporter) which is then used to “deliver” the new gene to the liver where it can start making its own factor.

Studies of gene therapy are currently being conducted in both hemophilia A and B by multiple pharmaceutical companies. Using adeno-associated virus (AAV) vectors, both the factor VIII and factor IX genes have been successfully transferred to patients with hemophilia. The AAV family of viruses is benign in humans, and almost everyone has been exposed by the time they reach adulthood. These beneficial viruses are liver-specific, and so deliver factor VIII and IX genes reliably to the organ which would normally produce those proteins.

The FIX gene is smaller and easier to package inside the viral vector, and therefore gene therapy for FIX deficiency is slightly farther along than that for FVIII deficiency. Some study subjects have shown a transient immune response to the AAV vector, which has successfully been treated with a brief course of steroids. Some strategies have employed the FIX-Padua gene mutation. FIX-Padua is a naturally-occurring mutation that was first identified in an Italian family with venous thrombosis found to be due to excessive levels of FIX. Using FIX-Padua in a gene therapy approach may result in higher FIX activity, to optimize FIX levels. Some subjects have shown sustained response years after the initial gene therapy was administered.

Development of factor VIII gene therapy is also underway. An abstract at the International Society on Thrombosis and Haemostasis Congress in Berlin reported FVIII levels in the normal range after a very high vector dose also using an AAV-based strategy. To get around the large size of the factor VIII gene, most gene therapy products employ a B-domain deleted variant of FVIII.

Studies of potential gene therapy for multiple other hematology disorders are in development. Von Willebrand disease may be the next target for such an approach. Vectors other than AAV are also being considered, including other viruses and non-viral options such as nanoparticles.

In addition to the above advances in treatment, scientists are engaged in other ways to manipulate the coagulation cascade to provide hemostasis to patients with bleeding disorders. Even if (or, more optimistically, when) gene therapy is successful for patients with hemophilia A and B, we will still have need of hemostatic treatments for those with rare bleeding disorders. It is a very exciting time to be involved in this area of medicine and very gratifying to be able to offer new options to patients for the treatment of their disorders.

Dr. Carpenter is Board certified in Pediatrics and Pediatric Hematology-Oncology. She is Associate Director of the Division of Hematology/Oncology/BMT at CMH, Section Chief of Hematology, Medical Director of the Kansas City Regional Hemophilia Treatment Center and the Anticoagulation Management Program at Children’s Mercy Hospital. Dr. Carpenter has a Masters in Clinical Investigation with experience designing and running clinical trials. She is active on many national committees and is also Associate Program Director for the Pediatric Hematology/Oncology fellowship at Children’s Mercy Hospital.

**REFERENCES**


What is a drug, as defined by the FDA?
A drug is any product that is intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease; and is intended to affect the structure or any function of the body.

PRE-CLINICAL
Drug Sponsor’s Discovery and Screening Phase:

Drug Developed
Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

Animals Tested
Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

IND Application
The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing. This application includes the drug's composition and manufacturing specifications, and offers a plan for testing the drug on humans.

IND Review:
FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protections.
Phase 1

20-80: The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal in this phase is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.

Phase 2

100s: The typical number of patients used in Phase 2; this phase emphasizes effectiveness. The goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

Phase 3

1000s: The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and use the drug in combination with other drugs.

FDA’s requirement for the number of patients needed to conduct a study/trial does change based on the size of the patient population being studied. For bleeding disorder studies/trials, counts are significantly reduced and sometimes can be fewer than 10 patients for Phase I trials. By Phase III, trials may include more than 100 people.

The objective: have a statistically relevant sample size from which to draw conclusions.

e.g., Two hundred trial participants in a hemophilia study is 1% of the US hemophilia population, whereas 1% of the US diabetic population in a diabetes study trial would equal 291,000 participants.
**Review Meeting**

FDA meets with a drug sponsor prior to submission of a New Drug Application (NDA).

**NDA Application**

The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

**Application Reviewed**

After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness.

**Drug Labeling**

FDA reviews the drug’s professional labeling and assures appropriate information is communicated to health care professionals and consumers.
Phase 4

Because it’s not possible to predict all of a drug’s effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA’s post-marketing safety system is meant to detect serious unexpected adverse events and take definitive action when needed.

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

FDA’s MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug’s labeling and the public is informed of the new information through letters, public health advisories, and other educational means. In some cases, the use of the drug might be substantially limited. And in rare cases, the drug might need to be withdrawn from the market.
Access Challenges for New Treatments

By Katie Verb, JD, Staff

With new products come new challenges in making sure patients have access to innovative therapies. Historically, health plans have afforded access to the full range of clotting factor products. Treatments have usually been exempt from Medicaid Preferred Drug Lists (PDLs) and from private formularies. Factor is often “carved out” of Medicaid Managed Care, ensuring that Managed Care Organizations (MCOs) are paid directly from the state for the clotting factor used by their patients.

Formularies and PDLs

Formularies: lists of drugs, often broken down into tiers with fixed dollar amounts or percentages that the patient is required to pay.

Prior Authorization

Prior authorization: a review process required by a health insurer to determine whether a treatment plan or prescription drug will be covered by the insurer.

Formularies and PDLs are tools health payers use to manage costs by steering patients toward preferred, and of course, lower-priced, medications. The terms “formulary” and “PDL” are often used interchangeably, but formulary is most typically associated with private health plans and PDL is associated with Medicaid. Formularies are lists of drugs, often broken down into tiers with fixed dollar amounts or percentages that the patient is required to pay. Since Medicaid does not charge copays or coinsurance, drugs on Medicaid PDLs are classified as either preferred or non-preferred. Once a health plan establishes its list of covered drugs, a patient who needs a drug not on the formulary or PDL must take other measures, such as getting prior authorization or satisfying a step therapy protocol, to access that drug. As new products come to market that have differing mechanisms of action (i.e., long-acting vs. short-acting factor replacement therapy), it becomes easier for payers to divide these drugs into different categories, and subject them to onerous “utilization management” restrictions. HFA strongly believes that the development of formularies and PDLs is never an appropriate management tool for people with bleeding disorders.

Prior Authorization

Prior authorization, also known as preauthorization, prior approval, or precertification, is a review process required by a health insurer to determine whether a treatment plan or prescription drug will be covered by the insurer. If a patient does not receive prior authorization, yet they wish to follow their doctor’s treatment protocol, they must pay for the treatment or procedure out of pocket. Problems with lengthy prior authorization account for 16 percent of reported access issues among patients with bleeding disorders, according to Project CALLS, HFA’s data collection initiative that seeks to understand how insurance access issues affect health outcomes. When burdensome prior authorization procedures are implemented, access to necessary treatments can be delayed unnecessarily.

Step Therapy

Step therapy: a tool that health plans use to try to limit their spending on prescription drug benefits.

Step therapy – sometimes called “fail first” – is a tool that health plans use to try to limit their spending on prescription drug benefits. After the formulary or PDL is developed, a patient who needs an off-formulary medication must first try, and fail on, one or more listed drugs before being approved for the non-listed medicine that their doctor believes will be the best treatment. HFA and other stakeholder groups have consistently maintained that step therapy is inappropriate in the context of bleeding disorders care. Hemophilia treatments are complex biological products and, as such, are not therapeutically
ADVOCACY IS IN YOUR BLOOD
equivalent or interchangeable. No one-size-fits-all product works equally well for all individuals. In addition, no clinical definition exists of what comprises failure for an individual using any given hemophilia product. And yet, as we know, the potential consequences of ineffective treatment (whether a major bleed, or cumulative damage from repeated bleeding episodes) are serious.

**Emerging Concerns**

HFA has been pushing back against the use of formularies and PDLs, burdensome prior authorization procedures, and step therapy in our community, through advocacy with payers and on the state and federal level. Looking ahead, we are concerned that new access issues will emerge once novel and gene therapies are available on the market.

One access concern is how statutory law governs coverage for bleeding disorders treatment by public payers, Medicaid and Medicare. For example, Medicare Part B covers treatment for hemophilia under a statute that expressly references the term “clotting factor.” As new therapies are available that do not operate exactly like clotting protein replacement therapy, how will those new drugs be covered? Medicare Part D medications come with a statutory 25-33 percent co-insurance for specialty drugs, a price tag that is too high for almost anyone in the aging community. Many state Medicaid programs also refer to clotting factor specifically, especially when referencing reimbursement for specialty pharmacies and hemophilia treatment centers (HTCs). How will those products and services, and reimbursement for them, be provided with novel and gene therapies?

Another concern is the high price tag for one-time treatments in the form of gene therapy or even for more traditional cures, as we saw for hepatitis C, a cure in the form of a one-time treatment that cost $80,000. One treatment for a rare enzyme disorder approved in Europe came with such a high price tag—$1 million per treatment—that most European payers refused to cover the therapy. The manufacturer ended up abandoning the product in both Europe and the United States. Given how often people switch insurance carriers, carriers might be reluctant to pay high upfront prices for treatments that may eventually benefit the patients’ subsequent insurers (in the form of better health outcomes and lower overall costs). When payers are determining whether to cover a new therapy (or if that therapy has “value” for its customers), therapies are assessed based on their cost versus the cost of previous treatments, however, many health economists believe that nontraditional metrics should be used when payers assess paying for emerging therapies. Suggested metrics include the cost of drug development and manufacture, the size of the treatable population, how the specific gene therapy is delivered, and the quality of the outcome measured over time.

HFA advocates for open access to every available treatment for people with bleeding disorders. As new therapies come to market, we will continue to monitor emerging access issues and will engage in the debate to protect coverage for our community from all payers, both public and private.

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Thank you!

This issue was made possible by the generous support of our funders.

HFA offers informative communication opportunities to funders in an effort to provide community members with information about products and therapies on the market.

The following pages contain funder-sponsored informative communications. Questions about the therapies discussed should be directed to your medical providers and the manufacturers.
He’s free to infuse only once every 14 days. Are you?

The only FDA-approved treatment for hemophilia B with up to 14-day dosing.* Visit us at IDELVION.com.

Protection with peace of mind—low incidence of side effects

*Durable people 12 years and older may be eligible for 14-day dosing. Talk with your doctor.
†Average FIX levels with 7-day dosing over 92 weeks in clinical trials.

Important Safety Information
IDELVION is used to control and prevent bleeding episodes in people with hemophilia B. Your doctor might also give you IDELVION before surgical procedures. Used regularly as prophylaxis, IDELVION can reduce number of bleeding episodes.

IDELVION is administered by intravenous injection into the bloodstream, and can be self-administered or administered by a caregiver. Do not inject IDELVION without training and approval from your healthcare provider or hemophilia treatment center.

Tell your healthcare provider of any medical condition you might have, including allergies and pregnancy, as well as all medications you are taking. Do not use IDELVION if you know you are allergic to any of its ingredients, including hamster proteins. Tell your doctor if you previously had an allergic reaction to any FIX product.

Stop treatment and immediately contact your healthcare provider if you see signs of an allergic reaction, including a rash or hives, itching, tightness of chest or throat, difficulty breathing, lightheadedness, dizziness, nausea, or a decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. You might need to be tested for inhibitors from time to time. IDELVION might also increase the risk of abnormal blood clots in your body, especially if you have risk factors. Call your healthcare provider if you have chest pain, difficulty breathing, or leg tenderness or swelling.

In clinical trials for IDELVION, headache was the only side effect occurring in more than 1% of patients (1.8%), but is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away, or if bleeding is not controlled with IDELVION.

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 prescribing information for IDELVION on next page.
IDELVION®, Coagulation Factor IX (Recombinant), Albumin Fusion Protein
Initial U.S. Approval: 2016

BRIEF SUMMARY OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IDELVION safely and effectively. Please see full prescribing information for IDELVION, which has a section with information directed specifically to patients.

What is IDELVION?
IDELVION is an injectable medicine used to replace clotting Factor IX that is absent or insufficient in people with hemophilia B. Hemophilia B, also called congenital Factor IX deficiency or Christmas disease, is an inherited bleeding disorder that prevents blood from clotting normally.

IDELVION is used to control and prevent bleeding episodes. Your healthcare provider may give you IDELVION when you have surgery. IDELVION can reduce the number of bleeding episodes when used regularly (prophylaxis).

Who should not use IDELVION?
You should not use IDELVION if you have had life-threatening hypersensitivity reactions to IDELVION or are allergic to:
- hamster proteins
- any ingredients in IDELVION

Tell your healthcare provider if you have had an allergic reaction to any Factor IX product prior to using IDELVION.

What must I know about administering IDELVION?
- IDELVION is administered intravenously, directly into the bloodstream.
- IDELVION can be self-administered or administered by a caregiver with training and approval from your healthcare provider or hemophilia treatment center. (For directions on reconstituting and administering IDELVION, see the Instructions for Use in the FDA-Approved Patient Labeling section of the full prescribing information.)

Your healthcare provider will tell you how much IDELVION to use based on your weight, the severity of your hemophilia B, your age, and other factors. Call your healthcare provider right away if your bleeding does not stop after taking IDELVION.

Blood tests may be needed after you start IDELVION to ensure that your blood level of Factor IX is high enough to properly clot your blood.

What are the possible side effects of IDELVION?
Allergic reactions can occur with IDELVION. Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

IDELVION might increase the risk of abnormal blood clots forming in your body, especially if you have risk factors for such clots. Call your healthcare provider if you experience chest pain, difficulty breathing, or leg tenderness or swelling while being treated with IDELVION.

A common side effect of IDELVION is headache. This is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

Please see full prescribing information, including FDA-approved patient labeling.

Based on November 2016 PI revision.

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1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com www.AFSTYLA.com

For adults and children with hemophilia A

REACH HIGHER
With the Long-lasting Protection of AFSTYLA

Important Safety Information

AFSTYLA is used to prevent and control bleeding episodes in people with hemophilia A. Used regularly (prophylaxis), AFSTYLA can reduce the number of bleeding episodes and the risk of joint damage due to bleeding. Your doctor might also give you AFSTYLA before surgical procedures.

AFSTYLA is administered by intravenous injection into the bloodstream, and can be self-administered or administered by a caregiver. Your healthcare provider or hemophilia treatment center will instruct you on how to do an infusion. Carefully follow prescriber instructions regarding dose and infusion schedule, which are based on your weight and the severity of your condition.

Do not use AFSTYLA if you know you are allergic to any of its ingredients, or to hamster proteins. Tell your healthcare provider if you previously had an allergic reaction to any product containing Factor VIII (FVIII), or have been told you have inhibitors to FVIII, as AFSTYLA might not work for you. Inform your healthcare provider of all medical conditions and problems you have, as well as all medications you are taking.

Immediately stop treatment and contact your healthcare provider if you see signs of an allergic reaction, including a rash or hives, itching, tightness of chest or throat, difficulty breathing, lightheadedness, dizziness, nausea, or a decrease in blood pressure. Your body can make antibodies, called inhibitors, against FVIII, which could stop AFSTYLA from working properly. You might need to be tested for inhibitors from time to time. Contact your healthcare provider if bleeding does not stop after taking AFSTYLA.

In clinical trials, dizziness and allergic reactions were the most common side effects. However, these are not the only side effects possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

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.

Zero inhibitors observed—Low incidence of side effects in clinical trials

In clinical trials, dizziness and allergic reactions were the most common side effects.

Visit the CSL Behring Coagulation team at Booth 14 during this year’s HFA Meeting to learn more!

*Annualized spontaneous bleeding rate in clinical trials (interquartile range [IQR]=0–2.4 for patients ≥12 years; 0–2.2 for patients <12 years).
AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain
For Intravenous Injection, Powder and Solvent for Injection
Initial U.S. Approval: 2016

BRIEF SUMMARY OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AFSTYLA safely and effectively. Please see full prescribing information for AFSTYLA, which has a section with information directed specifically to patients.

What is the most important information I need to know about AFSTYLA?
• Your healthcare provider or hemophilia treatment center will instruct you on how to do an infusion on your own.
• Carefully follow your healthcare provider’s instructions regarding the dose and schedule for infusing this medicine.

What is AFSTYLA?
• AFSTYLA is a medicine used to replace clotting Factor VIII that is missing in patients with hemophilia A.
• Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.
• Does not contain human plasma-derived proteins or albumin.
• Your healthcare provider may give you this medicine when you have surgery.
• Is used to treat and control bleeding in all patients with hemophilia A.
• Can reduce the number of bleeding episodes when used regularly (prophylaxis) and reduce the risk of joint damage due to bleeding.
• Is not used to treat von Willebrand disease.

Who should not use AFSTYLA?
You should not use AFSTYLA if you:
• Have had a life-threatening allergic reaction to it in the past.
• Are allergic to its ingredients or to hamster proteins.

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

What should I tell my healthcare provider before using AFSTYLA?
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 hamster proteins.
• Have been told you have inhibitors to Factor VIII (because this medicine may not work for you).

How should I use AFSTYLA?
• Administer directly into the bloodstream.
• Use as ordered by your healthcare provider.
• You should be trained on how to do intravenous injections by your healthcare provider or hemophilia treatment center. Once trained, many patients with hemophilia A are able to inject this medicine by themselves or with the help of a family member.
• Your healthcare provider will tell you how much to use based on your weight, the severity of your hemophilia A, and where you are bleeding.
• You may need to have blood tests done after getting to be sure that your blood level of Factor VIII is high enough to clot your blood.
• Call your healthcare provider right away if your bleeding does not stop after taking this medicine.

What are the possible side effects of AFSTYLA?
• Allergic reactions may occur. Immediately stop treatment and call your healthcare provider right away if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.
• Your body may form inhibitors to Factor VIII. An inhibitor is a part of the body’s defense system. If you form inhibitors, it may stop this medicine from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.
• Common side effects are dizziness and allergic reactions.
• These are not the only side effects possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

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

Please see full prescribing information, including full FDA-approved patient labeling. For more information, visit www.AFSTYLA.com

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany

for:
CSL Behring Recombinant Facility AG
Bern 22, Switzerland 3000
US License No. 2009

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

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.
Rooted in effective bleed control

Reaching to help more patient types than any other product

- **30 years of research and long-term clinical experience** has gone into NovoSeven® RT
  - Compassionate use, also known as expanded access, began in 1989
  - FDA approval received in 1999
- **NovoSeven® RT is used to treat more patient types than any other product**
  - Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults and children with:
    - Hemophilia A or B with inhibitors
    - Congenital factor VII deficiency
    - Glanzmann’s thrombasthenia with a decreased or absent response to platelet transfusions
  - Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults with acquired hemophilia
- **More than 70 trials and registries completed**, with a commitment to ongoing research

Visit [NovoSevenRT.com](http://NovoSevenRT.com) today to learn more.
Indications and Usage
NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is used for:
• Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and people with Glanzmann's thrombasthenia who have a decreased or absent response to platelet transfusions
• Treatment of bleeding and prevention of bleeding for surgeries and procedures in adults with acquired hemophilia

Important Safety Information

WARNING: BLOOD CLOTS
• Serious blood clots that form in veins and arteries with the use of NovoSeven® RT have been reported.
• Your healthcare provider should discuss the risks and explain the signs and symptoms of blood clots to you. Some signs of a blood clot may include pain, swelling, warmth, redness, or a lump in your legs or arms, chest pain, shortness of breath, or sudden severe headache and/or loss of consciousness or function.
• Your healthcare provider should monitor you for blood clots during treatment with NovoSeven® RT.

Warnings and Precautions
• NovoSeven® RT should be used with caution if you have an increased risk for blood clots, such as with disseminated intravascular coagulation (DIC), clogged arteries, crush injury, septicemia (an infection in the blood), uncontrolled bleeding after giving birth, history of heart disease, liver disease, limited movement following surgery, in elderly people, in newborns, or if you are taking aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) with NovoSeven® RT.
• Allergic reactions, including serious whole body allergic reactions, have been reported with NovoSeven® RT. Tell your healthcare provider if you are allergic to NovoSeven® RT, any of its ingredients, or mice, hamsters, or cows. If you think you are having an allergic reaction, call your healthcare provider right away. Some signs of allergic reaction may include shortness of breath, rash, itching, redness of the skin, and fainting/dizziness.
• People with Factor VII deficiency should be monitored by their healthcare provider for antibodies, which can cause NovoSeven® RT to stop working properly.

Side Effects
• The most common and serious side effects are blood clots.
• Tell your healthcare provider about any side effects that bother you or do not go away.

Use with Other Drugs
• Blood clots may occur if NovoSeven® RT is given with Coagulation Factor XIII (13).

Please see Brief Summary of Prescribing Information on the following pages.
NovoSeven® RT Coagulation Factor VIIa (Recombinant)
Rx only

BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: THROMBOSIS: Serious arterial and venous thrombotic events following administration of NovoSeven® have been reported. [See Warnings and Precautions] Discuss the risks and explain the symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. [See Warnings and Precautions] Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. [See Warnings and Precautions]

INDICATIONS AND USAGE: Indicated for: Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Ganzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets. Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia.

CONTRAINDICATIONS: None known.

WARNINGS AND PRECAUTIONS: Thrombosis: Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) and an uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy [See Adverse Reactions and Drug Interactions]. Exercise caution when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications. Monitor patients who receive NovoSeven® RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NovoSeven® RT or stop the treatment, depending on the patient’s condition. Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis have been reported with NovoSeven® RT. Administer NovoSeven® RT only if needed in patients with known hypersensitivity to NovoSeven® RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. Should symptoms occur, discontinue NovoSeven® RT, administer appropriate treatment and weigh the benefit/risk prior to restarting treatment with NovoSeven® RT.

Antibody Formation in Factor VII Deficient Patients: Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven® RT. If the factor VII activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. Laboratory Tests: Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation of achieving hemostasis. Assays of prothrombin time (PT/INR), aPTT, partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven® has been shown to produce the following characteristics: PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven® RT administration is unknown.

Table: Adverse Reactions Reported in ≥2% of the 298 Patients with Hemophilia A or B with Inhibitors

<table>
<thead>
<tr>
<th>Body System</th>
<th># of adverse reactions</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>(n=1,339 treatments)</td>
<td>(n=298 patients)</td>
</tr>
<tr>
<td>Platelets, Bleeding, and Clotting</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

ADVERSE REACTIONS: The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia. Clinical Trials Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice. Adverse reactions outlined below have been reported from clinical trials and data collected in registries. Hemophilia A or B Patients with Inhibitors: In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in ≥2% of the patients that were treated with NovoSeven® for 1,939 bleeding episodes (see Table Table below).

Serious adverse reactions included thrombosis, pain, thrombophlebitis, deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and abnormal hepatic function. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome. In two clinical trials evaluating safety and efficacy of NovoSeven® administration to hemophilia A or B patients, the following serious adverse reactions were reported: acute post-operative hemarthrosis (n=1), internal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=4). Immunogenicity: There have been no confirmed reports of inhibitory antibodies against NovoSeven® or FVII in patients with congenital hemophilia A or B with alloantibodies. The incidence of antibody formation is 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 NovoSeven® RT with the occurrence of antibodies to other products may be misleading. Congenital Factor VII Deficiency: Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven®. 70 patients for 124 bleeding episodes, surgeries, or procedures. 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against rFVIIa and FVII (n=1), localized phlebitis (n=1). Immunogenicity: In 75 patients with factor FVII deficiency treated with NovoSeven® RT, one patient developed IgG antibody against rFVIIa and FVII and FVIII. Patients with factor VII deficiency treated with NovoSeven® RT should be monitored for factor VII antibodies. The incidence of antibody formation is 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 NovoSeven® RT with the incidence of antibodies to other products may be misleading. Acquired Hemophilia: Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Of these, clots were included shock (n=3), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral artery occlusion, cerebral ischaemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome. Ganzmann’s Thrombasthenia: Data collected from the Ganzmann’s Thrombasthenia Registry (GTR) and the HTRS registry showed that 140 patients with Ganzmann’s Thrombasthenia (n=41) were treated with NovoSeven® RT, 10 of whom had previous clopidogrel therapy. Eleven serious adverse reactions occurred in 9 patients with Ganzmann’s Thrombasthenia: 8 thrombotic events (n=5), cerebrovascular accident (n=2), deaths (n=1) and dyspnea (n=1). Postmarketing Experience: The following adverse reactions have been...
identified during post approval use of NovoSeven®. 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.

### Table: Post Marketing Experience

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including anaphylactic shock, flushing, urticaria, rash, angioedema)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic events (including hepatic artery thrombosis, myocardial infarction, cerebral infarction, intestinal infarction, intracardiac thrombus, peripheral ischemia, portal vein thrombosis, myocardial ischemia, renal artery thrombosis)</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS:** Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates. The risk of a potential interaction between NovoSeven® RT and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Do not mix NovoSeven® RT with infusion solutions. Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII.

**USE IN SPECIFIC POPULATIONS:** Pregnancy: Risk Summary. There are no adequate and well-controlled studies using NovoSeven® RT in pregnant women to determine whether there is a drug-associated risk. Treatment of rats and rabbits with NovoSeven® in reproduction studies has been associated with mortality at doses up to 6 mg per kg body weight and 5 mg per kg body weight, respectively. At 6 mg per kg body weight in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg body weight, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg body weight of NovoSeven® gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven®. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation: Risk Summary. There is no information regarding the presence of NovoSeven® RT in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NovoSeven® RT and any potential adverse effects on the breastfed infant from NovoSeven® RT or from the underlying maternal condition.

Pediatric Use: Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. Hemophilia A or B with inhibitors: During the investigational phase of product development NovoSeven® was used in 16 children aged 0 to <2 years for 151 bleeding episodes, 27 children aged 2 to <6 years for 140 bleeding episodes, 43 children aged 6 to <12 for 375 bleeding episodes and 30 children aged 12 to 16 years for 446 bleeding episodes. In a double-blind, randomized comparison trial of two dose levels of NovoSeven® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors 20 children aged 0 to <12 and 8 children aged 12 to 16 were treated with NovoSeven® in doses of 35 or 70 micrograms per kg dose. Treatment was assessed as effective (definite relief of pain/tenderness as reported by the patient and/or a measurable decrease of the size of the hemorrhage and/or arrest of bleeding within 8 hours [rated as excellent = 51%], within 8-14 hours [rated as effective = 18%] or after 14 hours [rated as partially effective = 25%]) in 94% of the patients. NovoSeven® was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NovoSeven®. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 86%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 10/12 (83%) in the 35 mcg/kg dose group at 48 hours; effective hemostasis was achieved in 10/10 (100%) in the 90 mcg/kg dose group and 9/12 (75%) in the 35 mcg/kg dose group at 5 days. In the surgery trial comparing bolus (B) and continuous infusion (C) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely, or decreased substantially) intra-operatively, through the first 24 hours and at day 5. At the end of the study period (Postoperative day 10 or discontinuation of therapy) hemostasis in two patients in the B group was rated effective and hemostasis in one patient was rated as ineffective (defined as bleeding is the same or has worsened). Hemostasis in all three patients in the C group was rated as effective. Adverse drug reactions in pediatric patients were similar to those previously reported in clinical trials with NovoSeven®, including one thrombotic event in a 4 year old with internal jugular vein thrombosis after port-a-cath placement which resolved. Congenital Factor VII deficiency: In published literature, compassionate use trials and registries on use of NovoSeven® in congenital Factor VII deficiency, NovoSeven® was used in 24 children aged <12 years and 7 children aged 12 to 16 years for 38 bleeding episodes, 16 surgeries and 8 prophylactic regimens. Treatment was effective in 35% of bleeding episodes (<5% not rated) and 100% of surgeries. No thrombotic events were reported. A seven-month old exposed to NovoSeven® and various plasma products developed antibodies against FVIII and rFVIIa [See Adverse Reactions and Overdosage].

Thrombosthenia: In the Glanzmann’s Thrombasthenia Registry, NovoSeven® was used in 43 children aged 0 to 12 years for 157 bleeding episodes and in 15 children aged 0 to 12 years for 19 surgical procedures. NovoSeven® was also used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including NovoSeven® was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0 to 12 years and >12 to 16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0 to 16 years. No adverse reactions were reported in Glanzmann’s thrombasthenia children.

Geriatric Use: Clinical studies of NovoSeven® RT in congenital factor deficiencies and Glanzmann’s thrombasthenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

**OVERDOSAGE:** Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials. The following are examples of accidental overdose. One newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms per kg body weight). Following additional administration of NovoSeven® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. One Factor VII deficient male (83 years of age, 1111 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occupital stroke). One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainboro, NJ 08536, USA
1-877-NOVO-7777
www.NovoSevenRT.com
Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark
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KOVALTRY®, Antihemophilic Factor (Recombinant): THE CONFIDENCE TO TAKE CONTROL

For children, adolescents, and adults with hemophilia A

For more information, visit YourKOVALTRY.com

INDICATIONS

- KOVALTRY® is a medicine used to replace clotting factor (Factor VIII or antihemophilic factor) that is missing in people with hemophilia A.

- KOVALTRY® is used to treat and control bleeding in adults and children with hemophilia A. KOVALTRY® can reduce the number of bleeding episodes in adults and children with hemophilia A when used regularly (prophylaxis). Your healthcare provider may give you KOVALTRY® when you have surgery.

- KOVALTRY® is not used to treat von Willebrand Disease.

IMPORTANT SAFETY INFORMATION

- You should not use KOVALTRY® if you are allergic to rodents (like mice and hamsters) or any ingredients in KOVALTRY®.

- Tell your healthcare provider if you have heart disease or are at risk for heart disease.

- The common side effects of KOVALTRY® are headache, fever, and itchy rash.

- Allergic reactions may occur with KOVALTRY®. Call your healthcare provider right away and stop treatment if you get tightness of the chest or throat, dizziness, decrease in blood pressure, and nausea.

- Your body can also make antibodies, called “inhibitors,” against KOVALTRY®, which may stop KOVALTRY® 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.
**KOVALTRY® Dosing:** The recommended dose for routine prophylaxis in adults and adolescents is 20 to 40 IU of KOVALTRY® per kg of body weight 2x/week or 3x/week. The recommended dose for routine prophylaxis in children 12 years old and younger is 25 to 50 IU of KOVALTRY® per kg of body weight 2x/week, 3x/week, or every other day according to individual requirements.

**IMPORTANT SAFETY INFORMATION (CONT’D)**

- Tell your healthcare provider about any side effect that bothers you or that does not go away.
- Call your healthcare provider right away if bleeding is not controlled after using KOVALTRY®.

For additional important risk and use information, please see Brief Summary on following page.

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

**Talk to your doctor to see if KOVALTRY® is right for you.**
This leaflet summarizes important information about KOVALTRY with vial adapter. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about KOVALTRY. If you have any questions after reading this, ask your healthcare provider.

**Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.**

**What is KOVALTRY?**

KOVALTRY 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). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally. KOVALTRY is used to treat and control bleeding in adults and children with hemophilia A. Your healthcare provider may give you KOVALTRY when you have surgery. KOVALTRY can reduce the number of bleeding episodes in adults and children with hemophilia A when used regularly (prophylaxis). KOVALTRY is not used to treat von Willebrand Disease.

**Who should not use KOVALTRY?**

You should not use KOVALTRY if you
- are allergic to rodents (like mice and hamsters).
- are allergic to any ingredients in KOVALTRY.

**What should I tell my healthcare provider before I use KOVALTRY?**

- Tell your healthcare provider about all of your medical conditions.
- Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.
- Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.
- Tell your healthcare provider if you have been told that you have inhibitors to Factor VIII (because KOVALTRY may not work for you).

**What are the possible side effects of KOVALTRY?**

The common side effects of KOVALTRY are headache, fever and itchy rash. Allergic reactions may occur with KOVALTRY. Call your healthcare provider right away and stop treatment if you get tightness of the chest or throat, dizziness, decrease in blood pressure, and nausea.

Your body can also make antibodies, called “inhibitors,” against KOVALTRY, which may stop KOVALTRY 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.

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

**How do I store KOVALTRY?**

Do not freeze KOVALTRY.

Store KOVALTRY at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Within this period, KOVALTRY may be stored for a period of up to 12 months at temperatures up to +25°C or 77°F.

Record the starting date of room temperature storage clearly on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The product then expires after storage at room temperature for 12 months, or after the expiration date on the product vial, whichever is earlier. Store vials in their original carton and protect them from extreme exposure to light.

Administer reconstituted KOVALTRY as soon as possible. If not, store at room temperature for no longer than 3 hours.

Throw away any unused KOVALTRY after the expiration date.

Do not use reconstituted KOVALTRY if it is not clear.

**What else should I know about KOVALTRY and hemophilia A?**

Finding veins for injections may be difficult in young children. When frequent injections are required, your healthcare provider may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. These devices may result in infections. Medicines are sometimes prescribed for purposes other than those listed here. Do not use KOVALTRY for a condition for which it is not prescribed. Do not share KOVALTRY with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about KOVALTRY. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about KOVALTRY that was written for healthcare professionals.

**Resources at Bayer available to the patient:**

For Adverse Reaction Reporting, contact Bayer Medical Communications 1-888-84-BAYER (1-888-842-2937)

To receive more product information, contact KOVALTRY Customer Service 1-888-606-3780

Bayer Reimbursement HELPline 1-800-288-8374

For more information, visit www.KOVALTRY-us.com

Bayer HealthCare LLC
Whippany, NJ 07981 USA
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Discover more about IXINITY®

Visit IXINITY.com
A ONCE-WEEKLY SUBCUTANEOUS (GIVEN UNDER THE SKIN) INJECTION FOR
PEOPLE WITH HEMOPHILIA A WITH FACTOR VIII INHIBITORS

We extend our appreciation to the individuals, families, and healthcare providers
who participated in the clinical trials that led to the approval of HEMLIBRA®.
We thank you and celebrate with the community who made it a reality.

Discover HEMLIBRA.com

WHAT IS HEMLIBRA?
HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT HEMLIBRA?
HEMLIBRA increases the potential for your blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow your healthcare provider’s instructions regarding when to use an on-demand bypassing agent, and the dose and schedule you should use.

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to your kidneys, brain, and other organs. Get medical help right away if you have any of the signs and symptoms of TMA during or after treatment with HEMLIBRA.

- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in your arm, leg, lung or head. Get medical help right away if you have any of the signs or symptoms of blood clots during or after treatment with HEMLIBRA.

If aPCC (FEIBA®) is needed, talk to your healthcare provider in case you feel you need more than 100 U/kg of aPCC (FEIBA®) total.
**HOW SHOULD I USE HEMLIBRA?**

See the detailed “Instructions for Use” that comes with your HEMLIBRA for information on how to prepare and inject a dose of HEMLIBRA, and how to properly throw away (dispose of) used needles and syringes.

HEMLIBRA may interfere with laboratory tests that measure how well your blood is clotting and may cause a false reading. Talk to your healthcare provider about how this may affect your care.

**WHAT ARE THE OTHER POSSIBLE SIDE EFFECTS OF HEMLIBRA?**

The most common side effects of HEMLIBRA include: redness, tenderness, warmth, or itching at the site of injection; headache; and joint pain. These are not all of the possible side effects of HEMLIBRA.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of Medication Guide on the following page for more important safety information, including Serious Side Effects.
HEMLIBRA increases the potential for your blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow your healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule you should use. HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to your kidneys, brain, and other organs. Get medical help right away if you have any of the following signs or symptoms during or after treatment with HEMLIBRA:
  - confusion
  - stomach (abdomen) or back pain
  - weakness
  - nausea or vomiting
  - swelling of arms and legs
  - feeling sick
  - yellowing of skin and eyes
  - decreased urination

- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in your arm, leg, lung or head. Get medical help right away if you have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
  - swelling in arms or legs
  - cough up blood
  - pain or redness in your arms or legs
  - shortness of breath
  - numbness in your face
  - chest pain or tightness
  - eye pain or swelling
  - fast heart rate
  - trouble seeing

If aPCC (FEIBA®) is needed, talk to your healthcare provider in case you feel you need more than 100 U/kg of aPCC (FEIBA®) total.

**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT HEMLIBRA?**

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- Do not attempt to inject yourself or another person unless you have been taught how to do so by a healthcare provider.
- Your healthcare provider will prescribe your dose based on your weight. If your weight changes, tell your healthcare provider.
- If you miss a dose of HEMLIBRA on your scheduled day, you should give the dose as soon as you remember. You must give the missed dose before the next scheduled dosing day and then continue with your normal weekly dosing schedule. Do not double your dose to make up for a missed dose.
- HEMLIBRA may interfere with laboratory tests that measure how well your blood is clotting and may cause a false reading. Talk to your healthcare provider about how this may affect your care.

**WHAT ARE THE POSSIBLE SIDE EFFECTS OF HEMLIBRA?**

**The most common side effects of HEMLIBRA include:**
- redness, tenderness, warmth, or itching at the site of injection
- headache
- joint pain

These are not all of the possible side effects of HEMLIBRA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**HOW SHOULD I STORE HEMLIBRA?**

- Store HEMLIBRA in the refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Store HEMLIBRA in the original carton to protect the vials from light.
- Do not shake HEMLIBRA.
- If needed, unopened vials of HEMLIBRA can be stored out of the refrigerator and then returned to the refrigerator. HEMLIBRA should not be stored out of the refrigerator for more than 7 days at 86°F (30°C) or below.
- After HEMLIBRA is transferred from the vial to the syringe, HEMLIBRA should be used right away.
- Throw away (dispose of) any unused HEMLIBRA left in the vial.

Keep HEMLIBRA and all medicines out of the reach of children.

**GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF HEMLIBRA.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HEMLIBRA for a condition for which it was not prescribed. Do not give HEMLIBRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about HEMLIBRA that is written for health professionals.

**WHAT ARE THE INGREDIENTS IN HEMLIBRA?**

**Active ingredient:** emicizumab

**Inactive ingredients:** L-arginine, L-histidine, poloxamer 188, and L-aspartic acid.

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Because you are unique.
Pfizer Hemophilia Connect

Call one number to access all of our resources

The Pfizer Factor Savings Card*
$12,000 annual support for eligible patients in 4 simple steps—the card can be used to help cover copay, deductible, and coinsurance costs associated with Pfizer factor products.

Pfizer RxPathways†
Eligible patients can save up to $10,000 with this comprehensive assistance program that provides a range of support services.

Trial Prescription Program‡
A one-time, 1-month supply up to 20,000 IU of Pfizer product delivered at no cost to your door.

Community Resources
Learn about support programs like HemMobile™, Patient Affairs Liaisons, scholarship assistance, and the educational speaker series.

*Terms and conditions apply; visit PfizerFactorSavingsCard.com for complete terms and conditions. For commercially insured patients only, Medicare/Medicaid beneficiaries are not eligible. The Card cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription. The card will be accepted only at participating pharmacies. This coupon is not health insurance.

†The Pfizer RxPathways Savings Card is not health insurance. For a complete list of participating pharmacies, visit PfizerRxPathways.com or call the toll-free number 1.877.744.5675.

‡Terms and conditions apply. 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. You may also find help accessing Pfizer medicines by contacting the Pfizer RxPathways Program.
Creating the path for advancements in hemophilia gene therapy research

“It is incredible to think of what a transformative advance gene therapy could be – it has been my career focus for the past two decades to solve this challenge.”

Katherine A. High, M.D., President and Chief Scientific Officer

“I have treated patients with hemophilia for the last 35 years. The potential to improve the lives of patients and their loved ones is what drives me.”

Marc Carr, M.D., Head of Clinical Development

We recognize that the path to transforming the lives of patients takes curiosity, courage and drive. The resilience of the people we serve is our inspiration to push through barriers to success. With your continued support, Spark Therapeutics is striving to challenge the inevitability of genetic disease by discovering, developing and delivering treatments in ways unimaginable – until now.

LEARN MORE:
Visit www.sparktx.com/hemophilia, or contact patients@sparktx.com for more information.
“I’m proud to be part of the development of a new gene therapy approach to treat hemophilia B.”

DELIVERING ON THE PROMISE OF GENE THERAPY

Edwin, hemophilia B patient in AMT-060 gene therapy trial, Amsterdam, The Netherlands.
You asked, we listened

HFA knows how critical an early diagnosis is for treatment and quality of life for women and girls with a bleeding disorder.

That is why we created Sisterhood, a mobile app designed for women to track menstrual and non-menstrual bleeds and symptoms.

Information logged by the user is secure and accessible only to the user. The app has the ability to email secure information to the user to share with her medical provider.

New features include:

Recording details on product strength. Users may now note the strength of menstrual products used when logging menstrual bleeding by choosing the detailed data entry in the preferences tab.

More accurate blood loss score (PBAC score) for providers. Having more detailed information allows providers to more accurately assess blood loss that assists in diagnosis.

Ability to add a photo. • Spanish language option.

Other features of the app include:

Symptom logging/tracking • The ability to record and track treatments used
Reminder alerts for periods and treatments • A place to log and rate joint and/or muscle pain
Space to jot additional notes • A wealth of information on bleeding disorders and a variety of topics pertaining to women and bleeding disorders

It’s free and easy to use. Download it for FREE!
Registration Now Open! • www.hemophiliafed.org

“\"I enjoy the interaction. Not just between the speakers and the attendees, but among the attendees themselves.\"”

“The speakers know how to communicate with the Spanish-speaking community.”

“My favorite part of Symposium was the knowledgeable speakers who could easily and effectively answer the questions and concerns expressed during the presentations.”