**Long-Acting Factor Concentrates: The Next Leap Forward in Hemophilia Care Arrives**

Innovation is the calling card of the future. — Anna Eshoo

**BY KEITH BERMAN, MPH, MBA**

**FEW IN NUMBER** are successful collaborations between clinical scientists and industry that eventually transform a generally devastating or seriously debilitating chronic disease into a readily manageable condition compatible with a long and healthy life.

One such disorder is type 1 diabetes, which once committed most young victims to a life diminished by cardiovascular disease, retinopathy, neuropathy and nephropathy — the most serious results of chronic poorly controlled blood glucose. Numerous innovations relating to the form and delivery of insulin — multiple daily insulin injection (MDII), insulin products with varying onsets of action, continuous glucose monitoring and insulin pump therapy — have dramatically improved glucose control and long-term prognosis.

A succession of treatment advances over the last 40 years has similarly transformed the lives of children and adults with hemophilia. The transition in the early 1970s from transfused fresh frozen plasma or cryoprecipitate to self-administered plasma-sourced factor VIII (hemophilia A) and IX (hemophilia B) concentrates immediately translated into less severe bleeds and reduced long-term joint disease. Later development of validated pathogen separation and inactivation processes and recombinant human factor VIII and IX products have virtually eliminated HIV and hepatitis infection risk.

Beginning in the 1990s, prescription of long-term prophylaxis regimens to maintain the circulating factor VIII level above 1 percent to 3 percent of normal (and factor IX typically above 2 percent of normal) has helped patients with more severe disease sharply cut the number of breakthrough bleeding episodes. Under the care of a well-trained hemophilia treatment specialist, an infant male born today with a severe factor VIII deficiency can prophylactically self-administer factor VIII every other day to three times weekly* to minimize or avert serious bleeding events and irreversible joint damage, and live a long, active life.

But not unlike type 1 diabetics who maintain glycemic control with MDII therapy, a price must be paid by persons with hemophilia who commit to routine prophylaxis; the need for frequent self-injections. The diabetes management industry responded to needlestick-related treatment compliance problems and other shortcomings of MDII by developing continuous subcutaneous insulin infusion (CSII) by self-programmable insulin pumps and, very recently, the creation of a new inhalable insulin product used in conjunction with long-acting insulin. But for persons with hemophilia on a prophylaxis regimen, there is no option other than frequent intravenous (IV) self-administration of their factor product.

Today nearly two-thirds of persons with moderate or severe forms of hemophilia A, and one-third with hemophilia B, manage their disease with some form of prophylaxis. But, unfortunately, some fail to reliably adhere to their prescribed schedule of regular infusions of clotting factor. Poor compliance results in periods of subprotective levels of circulating factor VIII or IX and consequent breakthrough bleeding events. But even for those who have the discipline to do so, self-administration of their drug into a

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* Factor IX is generally dosed prophylactically two to three times weekly. The sole conventional recombinant factor IX approved for routine prophylaxis (RIXUBIS; Baxter Healthcare) is dosed twice weekly.
vein several times a week is an unpleasant and burdensome experience.

Of course the optimal solution is to cure hemophilia itself through gene therapy. A number of clinical and pre-clinical studies are currently in progress to investigate various gene therapy candidates, but prospects for approved treatments remain uncertain. For hemophilia A in particular, which accounts for about 80 percent of all persons with moderate and severe disease, safe and effective gene therapy remains many years away.

Meanwhile, the biopharmaceutical industry has pursued the next best option: Reduce the number of necessary infusions. As with other long-acting versions of approved biotherapeutics, this is achievable by variously modifying factor VIII or IX to persist longer in the circulation while still retaining the protein’s key functionality in the blood coagulation pathway. The need, as well as the commercial stakes involved, are well-appreciated: Five leading biopharmaceutical firms have invested heavily in development of eight proprietary long-acting factor VIII and IX product candidates.

**First Long-Acting Hemophilia Therapies Have Arrived**

In the race to introduce these products are most of the major suppliers of today’s conventional recombinant

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**Table 1. Long-Acting Factor VIII Products in the Development Pipeline**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Half-life extension technology</th>
<th>Development status</th>
<th>Selected findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAX 855</td>
<td>Baxter</td>
<td>PEGylation</td>
<td>Completed Phase III trial in 138 severe hemophilia A patients aged 12 years and older; evaluated on-demand treatment and twice-weekly prophylaxis. Application for FDA marketing approval expected before end of 2014.</td>
<td>1.5-fold increase in half-life over conventional recombinant factor VIII. Twice-weekly prophylaxis reduced ABR by 95 percent vs. on-demand treatment.</td>
</tr>
<tr>
<td>BAY 94-9027</td>
<td>Bayer</td>
<td>Site-specific PEGylation</td>
<td>Completed Phase II/III trial in 134 severe hemophilia A patients aged 12-65 years; evaluated on-demand treatment and prophylaxis twice weekly and every 5 and 7 days. Phase III study in previously treated children currently in progress.</td>
<td>1.5-fold increase in half-life over conventional recombinant factor VIII. All prophylaxis regimens sharply reduced ABR vs. ABR in subjects receiving on-demand treatment.</td>
</tr>
<tr>
<td>N8-GP</td>
<td>Novo Nordisk</td>
<td>GlycoPEGylation</td>
<td>Completed Phase III trial in 186 hemophilia A patients aged 12 years and older; evaluated prophylaxis every 4 days and on-demand regimens. Trials in children, PUPs, surgical procedures and as once-weekly prophylaxis currently in progress.</td>
<td>1.5-fold increase in half-life over conventional recombinant factor VIII. Prophylaxis reduced ABR by &gt;95% vs. ABR in subjects receiving on-demand treatment.</td>
</tr>
<tr>
<td>rFVIII-SingleChain (CSL627)</td>
<td>CSL Behring</td>
<td>Covalent binding of heavy and light factor VIII chains</td>
<td>Phase III trial in 200 subjects of any age with severe hemophilia A started in June 2014; testing prophylaxis and on-demand regimens. Phase III study in children with severe hemophilia up to age 11 years in progress.</td>
<td>Roughly 1.5-fold extended half-life vs. conventional recombinant factor VIII in primate pharmacokinetic study.</td>
</tr>
</tbody>
</table>

ABR: annualized bleeding rate  
PUPs: previously untreated patients  
VWF: von Willebrand factor
coagulation factors: Baxter, Bayer, CSL Behring and Novo Nordisk. But the first to secure regulatory approvals for its both long-acting factor VIII and factor IX products — Biogen Idec — turns out to be an entirely new entrant to the hemophilia therapy market. In March, the U.S. Food and Drug Administration (FDA) approved its ALPROLIX (Factor IX [Recombinant], Fc Fusion Protein), followed just three months later by approval of ELOCTATE (Antihemophilic Factor [Recombinant], Fc Fusion Protein).

Fusing the Fc portion of human IgG1 is believed to extend the half-life of these recombinant clotting proteins by exploiting the natural process that enables IgG to persist in the circulation for several weeks. Following endocytosis by vascular endothelial cells, the factor protein-bound constant Fc region of IgG1 binds to cellular neonatal Fc receptors (FcRn), which divert the protein-Fc complex away from lysosomal degradation and facilitate its return to the bloodstream (Figure 1). The half-life of Biogen Idec’s ALPROLIX factor IX fusion protein is about 86 hours, compared with about 26 hours for Baxter’s RIXUBIS and just under 19 hours for Pfizer’s BeneFIX recombinant factor IX products. The half-life of ELOCTATE, a much larger factor VIII fusion protein, is increased about 1.5-fold over the mean half-life of 12 hours for adults treated with Baxter’s ADVATE, the market-leading conventional recombinant factor VIII.

This Fc fusion technology is hardly new: The first of seven Fc fusion-based protein therapeutics approved in the U.S. over the last 15 years was the anti-tumor necrosis factor drug Enbrel (etanercept) in 1998, whose worldwide sales for treatment of autoimmune rheumatologic disorders now reportedly top $8 billion. Antibody-based therapeutics that utilize IgG1 Fc fusion to prolong half-life now account for about 20 percent of all licensed antibody-based medicines.

Whether long-acting or not, the therapeutic principle behind factor VIII or IX prophylaxis is the same: Keep the trough level of the missing clotting factor above a low threshold associated with increased bleeding risk. Pharmacokinetic simulations of Biogen Idec’s long-acting factor VIII found a clear association between number of days with a factor VIII activity under 1 international unit (IU)/dL and increased bleeding tendency. A mean of 224 out of 365 days under 1 IU/dL was documented in clinical trial subjects

### Table 2. Long-Acting Factor IX Products in the Development Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Half-life extension technology</th>
<th>Development status</th>
<th>Selected findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>rIX-FP</td>
<td>CSL Behring</td>
<td>Fusion protein with human albumin</td>
<td>Completed Phase II/III trial in 63 previously treated subjects with severe hemophilia B aged 12-65 years; evaluated weekly prophylaxis and on-demand regimens. Extension study and Phase III trial in children currently in progress.</td>
<td>Phase I/II study: mean 95-hour half-life (~4-fold increase over conventional recombinant factor IX)</td>
</tr>
<tr>
<td>N9-GP</td>
<td>Novo Nordisk</td>
<td>GlycoPEGylation</td>
<td>Completed Phase III trial in previously treated children up to age 12 years with moderately severe or severe hemophilia B; evaluating weekly prophylaxis. Phase III trial in previously untreated children currently in progress.</td>
<td>Phase III study: mean 110-hour half-life (~5-fold increase over conventional recombinant factor IX)</td>
</tr>
</tbody>
</table>

**Figure 1. Presumptive Mechanism of Factor IX Protein (rFIXFc) Half-Life Prolongation**

Bloodstream → Endothelial cell

- rFIXFc binds to FcRn receptor
- Lysosomal Degradation
- Lysosome
- rFIXFc recycled to bloodstream

The rFIXFc: Recombinant factor IX Fc fusion protein; same mechanism applies for rFVIIIFc (recombinant factor VIII fusion protein)
**ELOCTATE**

THE FIRST AND ONLY rFVIII WITH A PROLONGED HALF-LIFE

5 DAYS WITH FACTOR LEVELS ABOVE 1%

**MEAN FACTOR ACTIVITY PROFILE AFTER A SINGLE DOSE (50 IU/kg) IN ADULTS**

Mean terminal half-life after a single 50 IU/kg dose in pediatric and adolescent patients**†‡

- 16.4 (14.1, 18.6) hours in subjects 12 to 17 (n=11)
- 14.6 (11.5, 17.7) hours in subjects 6 to 11 (n=27)
- 12.0 (9.55, 14.4) hours in subjects 2 to 5 (n=10)

**Indications**

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

**Selected Important Safety Information**

- ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
**ELOCTATE Prophylaxis Starting With INFUSIONS EVERY 4 DAYS**

**Recommended starting regimen**

- 50 IU/kg administered every 4 days

- Regimen may be adjusted based on patient response in the range of 25-65 IU/kg at 3-5 day intervals
- More frequent or higher doses up to 80 IU/kg may be required in children <6 years of age

- After administering ELOCTATE, the one-stage clotting assay or chromogenic assay can be used to monitor plasma Factor VIII levels

**Potential For MORE TIME BETWEEN INFUSIONS**

- Among 112 subjects treated for ≥6 months, 29% achieved a dosing interval of ≥5 days during the last 3 months on study

**Important Safety Information**

**CONTRAINDICATIONS:** ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

**WARNINGS AND PRECAUTIONS:** Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Immediately discontinue ELOCTATE and initiate appropriate treatment if hypersensitivity reactions occur. Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Patients using ELOCTATE should be monitored for the development of Factor VIII inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor VIII levels have been achieved and maintained.

**ADVERSE REACTIONS:** Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

*Number of infusions may vary per individual.*

Please see Brief Summary of full Prescribing Information on the following pages.
With Individualized Prophylaxis
PROVEN PROTECTION* FROM BLEEDS

MEDIAN ANNUALIZED BLEED RATE†‡

<table>
<thead>
<tr>
<th></th>
<th>Individualized Prophylaxis (n=117)</th>
<th>On-Demand (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL BLEEDS</td>
<td>1.60 (0.00, 4.60)</td>
<td>0.00 (0.00, 1.11)</td>
</tr>
<tr>
<td>JOINT BLEEDS</td>
<td>22.76 (15.07, 39.02)</td>
<td>20.24 (12.27, 36.81)</td>
</tr>
<tr>
<td>SPONTANEOUS BLEEDS</td>
<td>0.00 (0.00, 2.03)</td>
<td>0.00 (0.00, 2.03)</td>
</tr>
</tbody>
</table>

*Protection is the prevention of bleeding episodes using a prophylaxis regimen.
† Median (interquartile range 25th and 75th percentiles).
‡ A-LONG, a multicenter, prospective, open-label, Phase 3 study (N=165), evaluating the safety and efficacy of ELOCTATE in previously treated male patients aged 12 to 65 years with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) that compared the efficacy of each of two prophylactic treatment regimens (individualized interval and fixed weekly) to episodic (on-demand) treatment. Hemostatic efficacy was determined in both: treatment of bleeding episodes and during perioperative management in subjects undergoing major surgical procedures. 164 and 163 subjects were evaluable for safety and efficacy, respectively. 146 and 23 subjects were treated for at least 26 weeks and 39 weeks, respectively.

ADDITIONAL PIVOTAL TRIAL RESULTS

Once-Weekly Prophylaxis—Not a labeled dosing regimen

MEDIAN ANNUALIZED BLEED RATE†‡

<table>
<thead>
<tr>
<th></th>
<th>Once-Weekly Prophylaxis (n=23)</th>
<th>On-Demand (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL BLEEDS</td>
<td>3.59 (1.86, 8.36)</td>
<td>1.93 (0.00, 7.62)</td>
</tr>
<tr>
<td>JOINT BLEEDS</td>
<td>22.76 (15.07, 39.02)</td>
<td>20.24 (12.27, 36.81)</td>
</tr>
<tr>
<td>SPONTANEOUS BLEEDS</td>
<td>1.93 (0.00, 7.62)</td>
<td>1.93 (0.00, 7.62)</td>
</tr>
</tbody>
</table>

OTHER SAFETY CONSIDERATIONS

Zero Inhibitors in the Clinical Trial, No Anaphylaxis Was Reported, And Low Incidence Of Adverse Reactions (ARs)

- Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests
- One subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter
- Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur
- The most common ARs in the Phase 3 clinical study were arthralgia and malaise (each 1.2%) and: abdominal pain, lower; abdominal pain, upper; angiopathy§; bradycardia; chest pain; cough; dizziness; dysgeusia; feeling cold; feeling hot; headache; hypertension; joint swelling; myalgia; procedural hypotension; and rash (each 0.6%). Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia

§Vascular pain after injection of study drug.

Find out more at ELOCTATEpro.com
**ELOCTATE™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein]**
Lyophilized Powder for Solution For Intravenous Injection.

**Brief Summary of Full Prescribing Information.**

**1 INDICATIONS AND USAGE**

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:
- Control and prevention of bleeding episodes,
- Perioperative management (surgical prophylaxis),
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

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

**4 CONTRAINDICATIONS**

ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

**5.2 Neutralizing Antibodies**

Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following exposure to ELOCTATE. Monitor patients for inhibitor development by appropriate laboratory tests. If the plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after initiation of ELOCTATE, suspect the presence of an inhibitor (neutralizing antibody). See Monitoring Laboratory Tests (5.3).

**5.3 Monitoring Laboratory Tests**

- Monitor plasma Factor VIII activity by performing a validated test (e.g., one-stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained. (See Dosage and Administration [2].)
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of ELOCTATE. Use Bethesda Units (BU) to report inhibitor levels.

**6 ADVERSE REACTIONS**

Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

**6.1 Clinical Trials Experience**

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

In the multi-center, prospective, open-label, clinical trial of ELOCTATE, 164 adolescent and adult, previously treated patients (PITPs, exposed to a Factor VIII containing product for ≥150 exposure days) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) received at least one dose of ELOCTATE as part of either routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. A total of 146 (89%) subjects were treated for at least 26 weeks and 23 (14%) subjects were treated for at least 39 weeks.

Adverse reactions (ARs) (summarized in Table 3) were reported for nine (5.5%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. Of these ARs, two subjects were withdrawn from study due to adverse reactions of rash and arthralgia.

In the study, no inhibitors were detected and no events of anaphylaxis were reported.

**Table 3: Adverse Reactions Reported for ELOCTATE (N=164)**

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Number of Subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Malaise</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Feeling cold</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Feeling hot</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>Arthralgia</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Joint swelling</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, lower</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, upper</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

**6.2 Immunogenicity**

Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No subjects developed confirmed, neutralizing antibodies to Factor VIII. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter.

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, comitant medications and underlying disease.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category C
Animal reproductive studies have not been conducted with ELOCTATE. It is not known whether or not ELOCTATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELOCTATE should be given to a pregnant woman only if clearly needed.

**8.3 Nursing Mothers**

It is not known whether or not ELOCTATE is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when ELOCTATE is administered to a nursing woman.

**8.4 Pediatric Use**

Pharmacokinetic studies in children have demonstrated a shorter half-life and lower recovery of Factor VIII compared to adults. Because clearance (based on per kg. body weight) has been shown to be significantly higher in the younger, pediatric population (2 to 5 years of age), higher and/or more frequent dosing based on body weight may be needed. (See Clinical Pharmacology [12.3].)

Safety and efficacy studies have been performed in 56 previously treated, pediatric patients <18 years of age who received at least one dose of ELOCTATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent safety and efficacy trials, and subjects <12 were enrolled in an ongoing pediatric trial. Twelve subjects (21%) were >8 years of age, 31 (55%) subjects were 6 to <12 years of age, and 13 subjects (23%) were adolescents (12 to <18 years of age). Interim pharmacokinetic data from a pediatric study of the 38 subjects <12 years of age showed that no dose adjustment had been required for patients ≥6 years old. Children age 2 to 5 years had a shorter half-life and higher clearance (adjusted for body weight); therefore, a higher dose or more frequent dosing may be needed in this age group. (See Clinical Pharmacology [12.3].)

**8.5 Geriatric Use**

Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 or over to determine whether or not they respond differently from younger subjects.

**17 PATIENT COUNSELING INFORMATION**

Advise the patients to:
- Read the FDA approved patient labeling (Patient Information and Instructions for Use)
- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing.
- Report any adverse reactions or problems following ELOCTATE administration to their healthcare provider.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII therapy because this may be a sign of inhibitor development.

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Cambridge, MA 02142 USA
U.S. License # 1697

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receiving solely on-demand treatment with ELOCTATE. The annualized period under 1 IU/kg was shortened to about 52 days in subjects managed with a fixed prophylactic dose of 65 IU/kg once weekly, and further shortened to just two days in subjects on individually tailored prophylactic regimens.

Thus, for each patient managed prophylactically with ELOCTATE or any factor concentrate, a balance must be found between increasing the time interval between infusions and maintenance of a protective clotting factor activity level. In the pivotal ELOCTATE clinical study, pharmacokinetic parameters were used to guide the dosing interval (every three to five days) and dose (25 to 65 IU/kg) in a group of subjects on individualized prophylaxis; the mean annualized bleeding rate (ABR) in this group was 95 percent lower than the ABR in the on-demand group. The ABR in a separate group managed with weekly prophylaxis at a fixed 65 IU/kg dose was 90 percent lower than the on-demand group — good, but still a meaningfully higher rate than the group on individualized prophylaxis. Consistent with these findings, the prescribing information for ELOCTATE advises physicians to start with 50 IU/kg every four days, then individualize dose and injection frequency based on patient response.

The practical advantage of ELOCTATE for patients is straightforward: A prophylaxis regimen can maintain a protective factor VIII level with fewer self-infusions than conventional recombinant factor VIII products while realizing similar benefits in reduced breakthrough bleeds compared with on-demand treatment. An individual who required conventional factor VIII dosing three times weekly, for example, may need to dose ELOCTATE only twice a week. Similarly, because its elimination half-life is several times longer than that of Pfizer’s BeneFIX, Baxter’s RIXUBIS or plasma-based factor IX products, including Alphanine SD and Mononine, the frequency of ALPROLIX prophylaxis can be significantly reduced.

Other Long-Acting Factors Advance Toward Approval

Biogen Idec currently offers the only licensed long-acting factor VIII and IX products, but that advantage is likely to be short-lived. Four investigational recombinant factor VIII and two recombinant factor IX products with extended half-lives are now in advanced clinical development (Tables 1 and 2). Half-life extension in four of these six products — Novo Nordisk’s “N8-GP,” Baxter’s “BAX 855” and Bayer Pharmaceutical’s “BAY94-9027” factor VIII products and Novo Nordisk’s “N9-GP” factor IX — is achieved by attaching long polymer chains of polyethylene glycol (PEG) to the therapeutic protein via a process of covalent conjugation known as PEGylation, or a variant method called glycoPEGylation. In addition to other benefits, these long PEG polymer strands shield the protein from exposure to proteolytic enzymes and immune clearance mechanisms, thus protecting its functionality and prolonging its intravascular persistence (Figure 2).

CSL Behring has pursued its own innovative approaches. The company has redesigned recombinant human factor VIII to covalently bond its heavy and light chains together (Figure 3). Its resulting “rVIII-SingleChain” molecule is both more intrinsically stable and has a much higher affinity for von Willebrand factor (VWF), further enhancing its stability in the circulation. CSL Behring’s long-acting recombinant factor IX exploits recombinant albumin fusion technology. Fusing albumin to factor IX creates at least two potential advantages: Albumin has a remarkably long intravascular half-life of about 20 days and, like the Fc portion of IgG1, it is unlikely to elicit unwanted immunogenicity. Albumin fusion technology has appeal as well from the production standpoint: A high-quality product can be manufactured with fewer post-expression modifications and purification steps than PEGylation, and it can be produced more efficiently.
than other fusion protein approaches, including use of the IgG1 Fc fragment. However, while numerous albumin fusion proteins are currently in clinical and preclinical development, to date just one therapeutic applying this technology has been approved for human use.**

Assuming most or all of these investigational products receive FDA marketing approval, we can expect an unusually spirited competition as new entrants strive to win over physicians and their patients. Most safety, pharmacokinetic and efficacy findings reported to date from the four investigational long-acting factor VIII agents are remarkably similar to those for Biogen Idec’s Fc fusion-based ELOCTATE. All appear to have about a 1.5-fold extended circulating half-life compared with conventional recombinant factor VIII. Phase III clinical trial data suggest that optimized prophylaxis with several of these could reduce the risk of breakthrough bleeds by around 95 percent in relation to episodic therapy — again quite similar to ELOCTATE.

**TANZEUM (albiglutide) (GlaxoSmithKline). TANZEUM is a GLP-1 receptor agonist indicated for use in adults with type 2 diabetes. Approved April 2014.**

**What Comes Next?**

For persons with hemophilia either on or contemplating a prophylaxis regimen, the arrival of this new generation of long-acting clotting factors will translate into a reduced self-infusion burden, much-improved likelihood of treatment compliance, fewer bleeding events, and reduced joint disease and related disability. Fewer units of factor will be infused, but offsetting this will be higher cost per unit.

Will extended half-life factor VIII and IX therapies turn out to be the last important wave of innovation we see from industry until gene therapy someday reduces or eliminates the need for replacement therapy altogether?

Don’t count on it. Researchers at Chugai Pharmaceuticals have developed a humanized bispecific monoclonal antibody, named ACE910, a primate model, a single bolus was shown to have potent hemostatic activity equivalent to a therapeutic dose of human factor VII.1

ACE910 has been in-licensed by Roche, and renamed RG6013. An 82-subject Phase I clinical trial of RG6013 is now in progress in Japan. Preliminary pharmacokinetic, safety and tolerability findings will be presented this December at the annual meeting of the American Society of Hematology in San Francisco. Should this Chugai/Roche factor VIII mimic prove to be safe and effective, consider these two features: It is dosed subcutaneously and appears to have a half-life of about three weeks.

As much as the extraordinary collaboration of clinical scientists and industry has done to improve health and the quality of life for persons with hemophilia, all indications suggest that more innovation yet lies ahead. 

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**References**


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**Five leading biopharmaceutical firms have invested heavily in development of eight proprietary long-acting factor VIII and IX product candidates.**

No safety-related concerns have been described for any of these six investigational long-acting coagulation factor therapies. With the exception of a single isolated instance, inhibitor antibodies in pivotal clinical trials of these investigational agents have not been reported. It is not unreasonable to expect that physicians designed to mimic the physiologic function of factor VIII by acting as a cofactor that promotes the activation of factor X by factor IXa. Importantly, it has been shown to be phospholipid-dependent, implying that its activity will be limited to the hemostatic site when introduced into the circulation. In

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**TANZEUM (albiglutide) (GlaxoSmithKline). TANZEUM is a GLP-1 receptor agonist indicated for use in adults with type 2 diabetes. Approved April 2014.**