Evolving Hemophilia Treatment Landscape
Expanding Treatment Options with Novel Therapies
Hemophilia A is a gene-related disease in which patients produce insufficient amounts of the blood clotting protein factor VIII. As a result, their blood is slow to clot after an injury, causing patients to often suffer spontaneous, painful bleeding into muscle tissue and joints. Hemophilia A affects one in 5,000 to 10,000 men — about 60 percent of them have severe disease (defined as having factor VIII activity less than one percent of normal).

Factor IX deficiency — or hemophilia B — affects one in 25,000 to 30,000 men. Approximately one-half have mild to moderate disease (differentiated by having factor IX activity above or below one percent of normal).

Treatment for hemophilia A consists of factor VIII replacement products (recombinant or plasma-derived) and, now, emicizumab (a monoclonal antibody that activates factor X). Treatment for hemophilia B consists of factor IX replacement products (also plasma-derived or recombinant). Additional varieties of recombinant products that have been introduced in recent years help increase the half-life, or duration of effectiveness, through fusion with stabilizing proteins and other changes.

### New Treatment Options

Since the 1990s, the standard of treatment for hemophilia A has been drugs called bypassing agents (BPAs), which made it possible to treat patients who had become resistant to conventional drug regimens. The last few years have seen the launch of several new long-acting hemophilia factor agents that have helped deliver significant benefits and treatment improvements for patients. Last fall, the U.S. Food and Drug Administration approved Hemlibra (emicizumab-kxwh) for the treatment of patients with hemophilia A with inhibitors. This month, it was approved for a new, wider indication among patients with hemophilia A without drug inhibitors, for biweekly as well as monthly administration.

Emicizumab offers a novel mechanism of action for prophylaxis to reduce bleeding episodes, as well as a subcutaneous route of administration and less frequent dosing (than use of intravenously administered factor VIII products for prophylaxis). Both of these characteristics are generally preferred by hemophilia A patients. However, it is just one among several promising new therapies in the hemophilia pipeline that could help change the treatment paradigm for patients, including many young children.

### Challenges of Hemophilia Treatment

Hemophilia A is typically treated by administering intravenous doses of the missing blood factor. Factor VIII replacement is employed both for the acute treatment of active bleeds and prophylactically to prevent bleeds from occurring. An estimated 20 to 30 percent of the roughly 15,500 patients with hemophilia A in the U.S. develop significant levels of these inhibitors.

Use of factor VIII may lead the body to produce antibodies — or inhibitors — against the drug, causing treatment to become ineffective.

Inhibitors increase the risk of bleeds and complications, as well as mortality, by rendering the most common factor replacement ineffective. They can be treated through immune tolerance induction (ITI) therapy, but the process is lengthy — it can take two years or more — and demanding. While the patient is undergoing ITI, bleeding episodes are typically treated with bypassing agents such as recombinant activated FVII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (APCC). These are expensive drugs — costing as much as $50,000 a dose — and some patients are treated prophylactically with them for the duration of ITI therapy, at a cost of $300,000 to $2.5 million per year.

Historically, inhibitor patients also have had a higher risk of comorbid complications including joint damage, pain, and increased risk of death. They are twice as likely to be hospitalized and their treatment costs are historically five times higher than noninhibitor patients, often exceeding $1 million annually.
High Cost, High Efficacy

Emicizumab is a monoclonal antibody that mimics the function of factor VIII in the blood clotting cascade, while eluding factor VIII inhibitors. The drug is self-administered once a week through subcutaneous injection and thus adjudicates under the pharmacy benefit. In clinical trials, it substantially lowered the rate of bleeding episodes in both inhibitor and non-inhibitor patients — which should lead to reductions in several important endpoints important to plan sponsors and patients alike: hospitalizations, long term joint damage (and other bleed complications), and cost variability.

Emicizumab is also very expensive: $482,000 for the first year and $448,000 per year after that. At least one recent pharmacoeconomic study found that over a lifetime, prophylaxis with emicizumab reduced total health care costs compared to BPA, while reducing bleeding episodes by more than half. But faced with upfront treatment costs of this level, payors still need to pay close attention to the patients selected to ensure the treatment is used only when appropriate.

Emicizumab’s effectiveness raises the possibility of using it in a variety of roles — for example, as a way to delay or completely avoid ITI therapy, or as a replacement for BPA while the patient is undergoing ITI therapy. With the approval of the additional indication for treatment of hemophilia A without inhibitors, it is likely to also play an important role in helping to prevent bleeding incidents in this larger population. Combined with its easier route of administration, this will further increase interest in utilization of the drug over time. In the larger context, though, some of the enthusiasm may be tempered as we draw nearer to the availability of other novel therapies that could require a less frequent, or even a one time, frequency of administration.

Managing Cost, Care

Novel drugs with a high price and a short history of clinical use can be difficult for payors to manage. Given that, it is crucial to understand acceptable and unacceptable uses of the drug, not just today, but on an ongoing basis. Prior authorization (PA) needs to be well-informed and sophisticated, especially because standards of care can be expected to evolve as the drug becomes more widely used and better understood. Our hemophilia PA program is set up to ensure that plan members meet the prescribing criteria for the current on-label use including, when appropriate, a prior history of high-inhibitor titer (confirmed by lab testing). Our approval criteria also takes into account member outcomes — whether members are achieving and maintaining a reduction in frequency of bleeding episodes.

Although emicizumab is generally well tolerated, there are some significant side effects and drug interactions — in clinical trials, some patients experienced thrombotic events when taking emicizumab in conjunction with APCC. Adherence can also often be a challenge with self-administered injectables. The program ensures that members have proper training, support, and follow-up, including digital medication reminders to help prevent non-adherence and adverse outcomes, and ensure they stay on therapy. We also evaluate the net price inclusive of all discounts/rebates as well as efficacy and tolerability when making coverage decisions.

Hemophilia patients vary widely in their needs, and it is of paramount importance to provide them with the support they need to use medications consistently and correctly. CVS Specialty provides that support through a dedicated, highly experienced Hemophilia Care Team, consisting of a clinical pharmacist, pharmacy service representative, pharmacy technician, clinical nurse coordinator and clinical nurse. This team provides consistent, high-touch care based on individual member needs. In addition, we also launched a Hemophilia Inhibitor Care Program, comprised of specialists from CVS Specialty, specifically to support hemophilia patients who have developed inhibitors and may be candidates for the new drug and other replacement factors.
Looking Forward

Though the number of hemophilia patients is small, the pipeline of new drugs for the condition is relatively rich. Many represent incremental improvements on current approaches, but there are also several drugs which use more cutting-edge technology, in trials.

- Fitusiran, an RNA-interference drug that “silences” part of the action of the gene responsible for hemophilia, is now in Phase III trials. It is projected to be a once-monthly injection that both inhibits antithrombins (which prevent clotting) and promotes production of thrombin (which encourages it). It is intended for use not just in hemophilia A, but in hemophilia B (which is caused by too-low levels of factor IX).

- Several gene therapies are in early-stage development. Their goal is to restore factor VIII production to normal levels without need of further treatment by inserting a corrected, functioning copy of the gene into cells. There are currently questions over durability of this approach (how well it will work over the long run) — several years or more — and researchers fear that it might not be appropriate for patients. Nonetheless, many clinicians, patients, and industry analysts are hopeful about the drugs’ prospects.

While it is unlikely that hemophilia A will become a curable disease in the foreseeable future, it is clear that treatment will continue to evolve, perhaps rapidly, over the next few years. This is good news for patients. For payors, it is a situation to monitor closely and respond to quickly. CVS Health stands ready to assist in that effort.