First Gene Therapy Approved for Hemophilia B

On November 22, 2022, the FDA approved Hemgenix® (etranacogene dezaparvovec-drlb**)**, the first gene therapy for treating hemophilia B, a rare inherited bleeding disorder. Hemophilia B is a lifelong bleeding disorder caused by a single gene defect that reduces the production of a protein called clotting factor IX (FIX). Although the disease is most often passed down from parents to children, about one-third of cases are caused by a spontaneous mutation or change in a gene. All races and ethnic groups are affected but men are the most likely to have symptoms. According to Centers for Disease Control data from federally funded hemophilia treatment centers during the past 10 years, there are approximately 6,000 male patients with hemophilia B in the United States. The severity of hemophilia B varies depending on the level of FIX produced by the patient. In milder cases, prolonged or heavy bleeding may only occur after an injury, surgery, or dental procedure. In severe cases, bleeding episodes can occur spontaneously without a clear cause. Patients may also experience prolonged bleeding in joints, muscles, and internal organs, which leads to pain, swelling, and joint damage. Frequent prophylactic FIX infusions can reduce joint bleeding events, prevent life-threatening bleeds, and help to preserve joint functions. Unfortunately, even with prophylactic therapy, unobservable, yet harmful micro-bleeds can still occur.

Hemginix is a single dose intravenous infusion that reduces the rate of abnormal bleeding by enabling the body to continuously produce Factor IX (FIX), a protein needed to form blood clots and stop bleeding. Specifically, Hemgenix utilizes a viral vector to deliver the genetic instructions for making Factor IX to target cells in the liver. Once delivered, the new genetic instructions remain in the target cells and generate factor IX proteins that are five to eight times more active than normal. Current hemophilia B patients may require prophylactic intravenous infusions of factor IX up to several times per week which cost approximately $550,000 to $750,000 annually. The approval of Hemgenix provides a one-time treatment alternative to the routine FIX injections. According to the manufacturer CSL Behring, Hemgenix will cost $3.5 million, making it the most expensive medication approved to date. The price does not include treatment-related costs incurred at treatment centers or costs associated with patient monitoring.

The approval of Hemgenix was supported by results from the ongoing Phase 3, single arm, single dose HOPE-B trial. Fifty-four adult male patients classified as having moderately severe to severe hemophilia B and requiring prophylactic FIX replacement therapy were enrolled in a prospective, six-month observational period during which time they continued to use their current standard of care therapy to establish a baseline annualized bleeding rate (ABR). The annualized bleeding rate for each patient is the number of bleeding episodes in the 12-month period. Moderate to severe hemophilia was defined as less than or equal to 2 percent of normal FIX activity. After the six-month lead-in period, patients received a single intravenous administration of Hemgenix. The primary endpoint in the pivotal study was noninferiority of the 52-week ABR after achievement of stable FIX expression compared with the six-month lead-in period. For this endpoint, ABR was measured from month 7 to month 18 after infusion ensuring the observational period represented likely steady-state transgene expression. Hemgenix allowed patients to produce mean FIX activity of 39% at 6 months and 36.7% at 24 months post infusion. These factor levels correspond to mild hemophilia. Seven to 18 months post infusion, the mean adjusted ABR for all bleeds was reduced by 54% compared to the 6-month lead-in period on FIX prophylactic replacement therapy (from 4.1 to 1.9). Among study participants, 74% had bleeds in the lead-in period and 37% had bleeds 7 to 18 months after Hemgenix treatment. One of the key findings and potential real-life application from the clinical study was the finding that 94% of subjects treated with Hemgenix

discontinued use of FIX prophylaxis with an overall 97% reduction in mean annualized FIX consumption from lead-in period to months 13 thru 18. By reducing the number of bleeding episodes and the need for prophylactic therapy, the gene therapy significantly reduces the high burden of the disease and improves quality of life.

The durability of the clotting activity effect remains a concern with Hemgenix, but to date, data has been initially seen as positive. Behring has observed that FIX levels have been maintained up to 24 months after initiation of therapy with no sign of patients developing inhibitors against the infusion. An inhibitor is an immune response to infused clotting factors that renders standard factor replacement therapy ineffective. An estimated 1 to 4% of those with severe hemophilia B may develop an inhibitor.

In clinical trials, the most common adverse reactions associated with Hemgenix included liver enzyme elevations, headache, mild infusion-related reactions, and flu-like symptoms. Nine patients needed steroids for liver enzyme elevations. The trial was temporarily halted due to a case of liver cancer, but it was ultimately deemed not to be related to treatment.

Hemophilia B is an expensive disease to treat. The lifetime cost for ongoing routine prophylactic treatment can reach as high $20 million. In November 2022, the Institute of Clinical and Economic Review (ICER) posted an evidence report assessing the comparative clinical effectiveness and value of Hemgenix for hemophilia B. Their clinical findings indicate that patients treated with Hemgenix had an 80% reduction in treated joint bleeds and similar reductions in other bleeds when compared with their bleeding rates on FIX prophylaxis prior to gene therapy. However, the report did acknowledge there is still considerable uncertainty about the duration of benefit and adverse events with Hemgenix. The ICER cost-effectiveness modeling does show health gains and substantial cost offsets by eliminating the need for very expensive prophylactic treatment and concluded that Hemgenix would achieve the common thresholds for cost effectiveness if priced close to $2.9 million. The $3.5 million price tag is higher than the ICER cost effective threshold but over $16 million less than estimated lifetime costs for prophylactic factor IX therapy if durability of response is maintained for the patient's lifetime. ICER estimates that approximately 860 patients in the United States would be eligible for treatment based on the FDA approved indication with 20% initiating treatment in each of the next 5 years.

Current therapeutic options for hemophilia B are effective but require patients to adhere to strict, lifelong infusion schedules. Spontaneous bleeding episodes as well as limited mobility, joint damage or severe pain are still possible as a result of the disease. For appropriate patients, a single Hemgenix infusion offers a new treatment option that appears to provide patients living with hemophilia B the ability to produce their own sustained and elevated levels of factor IX, while reducing or eliminating the need for prophylactic therapy. The freedom for patients and caregivers from the need for regular, ongoing infusions is significant and potentially life altering. The $3.5 million price tag cannot be ignored, but the cost may be offset by potentially eliminating ongoing FIX prophylaxis therapy. If Hemgenix can maintain a therapeutic FIX activity for years to come without causing serious adverse effects, the treatment paradigm for hemophilia B will likely change. Other gene therapies are in the pipeline for hemophilia, including Roctavian™ (valoctocogene roxaparvovec) for hemophilia A. The FDA's approval decision for Rockavian is expected by June 2023, and if finally approved after earlier non-approval decisions, may also alter the treatment landscape for hemophilia A. The anticipated cost is expected to be similar to Hemgenix.

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