On June 29, 2023, BioMarin announced the FDA approval of Roctavian (valoctocogene roxaparvovec-rvox), for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA-approved test.

Hemophilia A is a blood disorder caused by a mutation in the gene responsible for producing a protein called factor VIII, which is necessary for blood clotting. Patients with severe hemophilia A are at risk for painful and potentially life-threatening bleeds, which can occur spontaneously.

- Approximately 1 in 10,000 people have hemophilia A and about 50% of patients with the condition have severe disease.
- BioMarin expects approximately 2,500 adults in the U.S. to be eligible to receive Roctavian.

Roctavian is the first gene therapy approved for hemophilia A. Roctavian works by delivering a functional gene that is designed to enable the body to produce factor VIII on its own, reducing the need for ongoing prophylaxis.

The efficacy of Roctavian was established in an open-label, single-dose, single-arm study in 134 adult males (18 years of age and older) with severe hemophilia A, who received a single intravenous (IV) dose of Roctavian. Of the 134 patients who received Roctavian, 112 patients had baseline annualized bleeding rate (ABR) data prospectively collected during a period of at least six months on factor VIII prophylaxis prior to receiving Roctavian (rollover population). The primary outcome was a non-inferiority (NI) test of the difference in ABR in the efficacy evaluation period (EEP) following Roctavian administration compared with ABR during the baseline period in the rollover population.

- The mean EEP ABR was 2.6 bleeds/year, compared to a mean baseline ABR of 5.4 bleeds/year. The mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The NI analysis met the pre-specified NI margin.

Roctavian is contraindicated in patients with:

- Active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B)
- Known significant hepatic fibrosis or cirrhosis
- Patients with known hypersensitivity to mannitol.

Warnings and precautions for Roctavian include infusion-related reactions; hepatotoxicity; thromboembolic events; monitoring laboratory tests; and malignancy.

The most common adverse reactions (≥ 5%) with Roctavian use were nausea, fatigue, headache, infusion-related reactions, vomiting, and abdominal pain. The most common laboratory abnormalities (≥ 10%) were alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, factor VIII activity levels, gamma-glutamyl transferase and bilirubin > upper limit of normal.

The recommended dose of Roctavian is $6 \times 10^{13}$ vector genomes per kilogram (vg/kg) body weight, administered as a single IV infusion.

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— Testing for pre-existing antibodies to AAV5 should be performed using the FDA approved companion diagnostic. Roctavian should not be administered to patients with a positive test for antibodies to AAV5. Information on FDA-approved tests for the detection of antibodies to AAV5 is available at: [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

— Refer to the Roctavian drug label for complete dosing and administration recommendations.

- The wholesale acquisition cost (WAC) for Roctavian will be $2.9 million for a one-time dose.

- BioMarin launch plans for Roctavian are pending. Roctavian will be available as a $2 \times 10^{13}$ vg/mL suspension for intravenous infusion.