Givlaari® (givosiran) – New orphan drug approval

- On November 20, 2019, the FDA announced the approval of Alnylam's Givlaari (givosiran), for the treatment of adults with acute hepatic porphyria (AHP).

- AHP refers to a family of ultra-rare genetic diseases that lead to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver. Severe, unexplained abdominal pain is the most common symptom, which can be accompanied by limb, back, or chest pain, nausea, vomiting, confusion, anxiety, seizures, weak limbs, constipation, diarrhea, or dark or reddish urine.

    - Long-term complications and comorbidities of AHP can include hypertension, chronic kidney disease or liver disease including hepatocellular carcinoma.
    - Currently, the population of AHP patients with diagnosed, active disease in the U.S. and Europe is estimated to be approximately 3,000.

- Givlaari is a first-in-class, small interfering RNA agent that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver *ALAS1* mRNA. This leads to reduced circulating levels of the neurotoxic intermediates associated with attacks and other disease manifestations of AHP.

- The efficacy of Givlaari was established in the ENVISION trial, a randomized, double-blind study in 94 patients with AHP. Patients were randomized to receive Givlaari or placebo during. Efficacy in the 6-month double-blind period was measured by the rate of porphyria attacks that required hospitalizations, urgent healthcare visit, or intravenous hemin administration at home.

    - The mean rate of porphyria attacks was 1.9 and 6.5 for Givlaari and placebo, respectively. This represented a 70% (95% CI: 60, 80) reduction in porphyria attacks for patients receiving Givlaari vs. placebo.
    - The mean number of days of hemin use was 4.7 (95% CI: 2.8, 7.9) with Givlaari vs. 12.8 (95% CI: 7.6, 21.4) with placebo.

- Warnings and precautions for Givlaari include anaphylactic reactions, hepatic toxicity, renal toxicity, and injection site reactions.

- The most common adverse reactions (≥ 20%) with Givlaari use were nausea and injection site reactions.

- The recommended dose of Givlaari is 2.5 mg/kg administered via subcutaneous (SC) injection once monthly. Dosing is based on actual body weight.

    - Givlaari is intended for SC use by a healthcare professional only.
    - Medical support should be available to appropriately manage anaphylactic reactions when administering Givlaari.

- The estimated wholesale acquisition cost (WAC) for Givlaari is $575,000 per year.

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- Alnylam is expected to make Givlaari available for shipment to healthcare providers by year-end. Givlaari will be available as a ready-to-use solution in single-dose vials of 189 mg/mL.