New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Givlaari ™ (givosiran) [**Alnylam Pharmaceuticals, Inc.**]**
Dosage Formulations:	189mg/ml single dose vial for subcutaneous injection
FDA Approval Date: **FDB File Date:**	FDA: November 20, 2019 FDB: December 1, 2019
Indication:	Acute hepatic porphyria (AHP) in adults
Mechanism of Action:	Givlaari is a double-stranded small interfering RNA 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 neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.
Dose/ Administration:	2.5mg/kg once monthly by subcutaneous injection administered by a healthcare professional only – dosing is based on actual body weight

Drug Clinical Highlights:	• Givlaari is only the second drug to be approved leveraging RNAi (RNA interference).
	  ○ The first was also an Alnylam product, Onpattro® (patisiran), which launched in August 2018 for polyneuropathy in hATTR amyloidosis
	  ○ RNAi is a natural cellular process of gene silencing that was recognized with the 2006 Nobel Prize for Physiology or Medicine
	  ○ Small interfering RNA (siRNA), molecules that mediate RNAi, function by potently silencing messenger RNA (mRNA) that encode for disease-causing proteins, thus preventing them from being made
	  ○ Alnylam is leading the translation of RNAi into a whole new class of innovative medicines, known as RNAi therapeutics, with a deep pipeline including five candidates that are in late-stage development
	• The FDA approved Givlaari in less than four months after acceptance of the NDA; approval was based on positive results from the ENVISION Phase 3 study
	  ○ ENVISION was a randomized, double-blind, placebo-controlled, multinational study in 94 patients with AHP with a minimum of 2 porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in the 6 months prior to study entry
	  ○ On average, AHP patients on Givlaari experienced 70% fewer porphyria attacks compared to placebo and 77% fewer annualized days on hemin
	  ○ Givlaari treated patients were shown to be on track for an expected average of 3.2 porphyria attacks per year after six months, versus an anticipated average of 12.5 attacks per year for the placebo arm
	  ○ 50% of Givlaari-treated patients were attack-free during the six-month treatment period as compared to 16.3% for placebo
	• Warnings:
	  ○ Anaphylactic Reaction
	  ▪ Occurred in <1% of patients in clinical trials
	  ▪ Must be administered by a healthcare professional
	  ▪ Medical support to appropriately manage anaphylactic reactions during administration must be present at the time of administration
	  ○ Hepatic Toxicity
	  ▪ ALT at least 3 times the upper limit of normal occurred in 15% of patients in clinical trials, primarily after 3-5 months of therapy
	  ▪ LFTs must be obtained prior to initiating therapy, monthly during the first 6 months of therapy, and then as clinically indicated thereafter
	  ▪ For severe or clinically significant ALT elevations, therapy should be interrupted or discontinued

	▪ Following therapy interruption with subsequent improvement in LFTs, therapy may be resumed at a dose of 1.25mg/kg once monthly ▪ If ALT elevations do not reoccur at the lower dose, the dosage may be increased back to 2.5mg/kg once monthly ○ Renal Toxicity ▪ Increases in serum creatinine levels and decreases in eGFR occurred in 15% of patients in clinical trials ▪ Monitor renal function during therapy as clinically indicated ▪ Dosage reduction in renal impairment is not necessary for Givlaari ○ Injection Site Reactions ▪ Includes erythema, pain, pruritus, rash, discoloration, and swelling at the injection site ▪ Occurred in 25% of patients in clinical trials • Adverse Reactions (other than those listed in above warnings): ○ Nausea occurred in 27% of patients in clinical trials ○ Fatigue occurred in 10% of patients in clinical trails • Drug Interactions: Givlaari increases the concentration of CYP1A2 or CYP2D6 substrates. Affected substrate agents should be discontinued or dosages decreased if used concomitantly with Givlaari.
Disease State Clinical Highlights:	• Porphyria refers to a group of at least 8 inherited metabolic disorders that arise as a result of a malfunction in the synthesis of heme, which is essential for the transport of oxygen to cells in the body • The prevalence of porphyria remains unknown, but clinicians suggest a range of 1 in 500 – 50,000 is probable • AHP is comprised of four types of porphyrias: acute intermittent porphyria, hereditary coproporphyria, variegate porphyria and ALA dehydratase-deficiency porphyria • Most individuals who inherit the gene for AHP seldom have symptoms, especially if certain preventative measures are taken concerning areas such as medications and diet • AHP disproportionately affects women of working and childbearing age • Symptoms of AHP vary widely but typically occur as intermittent attacks, which may be life-threatening due to neurologic complications such as seizures or paralysis • Approximately 20% of patients with recurrent symptoms develop chronic and ongoing pain and other symptoms • Approximately 3-5% of patients have frequent attacks, defined as more than 4 attacks per year, for a period of many years • Symptoms of AHP include severe, unexplained abdominal pain (most common) which may be accompanied by limb, back, or chest pain, nausea, vomiting, confusion, anxiety, seizures, limb weakness, constipation, diarrhea, or dark, reddish urine. These nonspecific symptoms result in mean delay in diagnosis of approximately 15 years. • Long-term complications of AHP include hypertension, chronic kidney disease, and liver disease (including hepatocellular carcinoma)
Price Per Unit (WAC):	• $39,000 per 189mg/ml single dose vial • Patients 75kg and less: $468,000 per year • Patients >75kg and ≤ 150kg: $936,000 per year • The manufacturer has stated that the average cost should be $575,000 per person per year, with an after discount cost of $442,000
Therapeutic Alternatives:	• Therapy for AHP attacks consists of hemin (Panhematin®) given IV once daily for 4 days ($30,687.84 per attack for a 75kg patient at normal dosing of 4mg/kg/day) • Other long-term management considerations for AHP therapy include discontinuation of medications that are harmful to patients during acute attacks, cigarette avoidance, alcohol avoidance, marijuana avoidance, and maintaining a diet high in carbohydrates (60-70% of total calories)

Prior Authorization Approval Criteria:	**Must meet the following criteria:**
	
	Initial Therapy:
	• Participant aged 18 years or older **AND**
	• Prescribed by or in consultation with a hepatologist, gastroenterologist, or other specialist in the treated disease state **AND**
	• Documented diagnosis of AHP (ICD10 E80.2X)
	  ○ Documentation of labs used to verify diagnosis such as spot or 24 hour urine delta-aminolevulinic acid (ALA), porphobilinogen (PBG), and creatinine with results 4 times the upper limit of normal **OR**
	  ○ Documentation of family history of AHP **OR**
	  ○ Documentation of genetic testing confirming the presence of a mutation for AHP **AND**
	• Documentation of active disease defined as at least 2 porphyria attacks within the past 6 months (defined by hospitalization, urgent healthcare visit, or intravenous hemin therapy) **AND**
	• Documentation of current LFTs and serum creatinine
	
	Continuation of Therapy:
	• Documentation of stabilized or decreased AHP attack frequency (i.e. decreased hospitalizations, urgent healthcare visits, or hemin therapy) **AND**
	• Documentation of current LFTs and serum creatinine (monthly during the first 6 months of therapy and then at least once annually)
	
	Additional Provider Diagnostic/Monitoring Criteria, if desired:
	• Ensure appropriate counseling is offered to the patient on how medications, nutrition, alcohol usage, stress, physical fatigue, and environmental factors may affect their disease state

Implication to State Medicaid Program:	• Expected LOE: TBD • Alnylam has stated that they expect about 3,000 people in the United States and Europe to be eligible for Givlaari • Alnylam has stated they are in talks with leading payers about value-based agreements for Givlaari and they plan to incorporate a new "ultra-rare disease framework" as part of its negotiations. Under the framework, participating government and commercial payers will pay the full value for the treatment "only when it delivers patient outcomes in the real-world setting similar to results demonstrated in clinical trials". • In addition, an additional prevalence-based adjustment feature will trigger rebates to participating payers "if the number of diagnosed patients they cover exceeds current epidemiologic estimates" for the condition.

References:

1. GIVLAARI™ (givosiran) injection, [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; November 2019.
2. PANHEMATIN® (hemin for injection) [package insert]. Raleigh, NC: Xellia Pharmaceuticals USA, LLC; July 2017
3. American Porphyria Foundation. https://www.porphyriafoundation.org/. Accessed December 9, 2019.
4. National Organization for Rare Disease. Porphyria. https://rarediseases.org/rare-diseases/porphyria/. Accessed December 9, 2019.
5. Wang, B, et al. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatology Communications, Vol 3, Issue 2. December 20, 2018. https://doi.org/10.1002/hep4.1297
6. FDA Approves Givlaari. https://www.drugs.com/newdrugs/fda-approves-givlaari-givosiran-acute-hepatic-porphyria-5109.html. Accessed December 9, 2019.
7. IPD Analytics. Hematologic: Porphyria. Accessed December 9, 2019.
8. IPD Analytics. New Drug Review: Givlaari (givosiran). December 2019.