

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212194Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name	Mei-Yean Chen, Pharm.D.
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Review Completion Date	November 1, 2019
Subject	Evaluation of Need for a REMS
Established Name	Givosiran
Trade Name	Givlaari
Name of Applicant	Alnylam Pharmaceuticals, Inc.
Therapeutic Class	A small interfering ribonucleic acid (siRNA)
Formulations	189 mg/ml in a single-dose vial
Dosing Regimen	2.5 mg/kg once monthly by subcutaneous injection

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Givlaari (givosiran) is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals, Inc. (Alnylam) submitted a New Drug Application (NDA) 212194 for givosiran with the proposed indication for the treatment of adults with acute hepatic porphyria administered as a monthly injection. The risks associated with givosiran include anaphylactic reaction, hepatic toxicity, renal toxicity, and injection site reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK believes that a REMS is not needed to ensure the benefits of givosiran outweigh its risks. Acute hepatic porphyria may manifest as acute attacks that produce serious abdominal, psychiatric, neurological, or cardiovascular symptoms. The intermittent attacks are sometimes life-threatening due to neurologic complications, such as seizures and paralysis. There is an unmet need for a maintenance therapy to prevent recurrent AHP attacks. The concerned risks associated with the use of givosiran, include anaphylactic reactions, hepatic toxicity, renal toxicity, and injection site reactions and will be communicated in the prescribing information in Section 2 Dosage and Administration, as well as Section 5 Warnings and Precautions. At the time of this review, the draft labeling for givosiran does not include a box warning for any of the aforementioned risks. Healthcare professionals who are likely to prescribe givosiran are expected to be familiar with the risks and management of anaphylactic reaction, hepatic/renal toxicities, and injection site reactions.

1 Introduction

This review evaluates whether a REMS for the NME Givlaari (givosiran) is necessary to ensure the benefits outweigh its risks. Alnylam submitted a NDA 212194 for givosiran with the proposed indication for the treatment of adults with acute hepatic porphyria (AHP). This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Givlaari (givosiran), an NME, is an aminolevulinic acid synthase 1-directed small interfering ribonucleic acid (siRNA) proposed for the treatment of adults with AHP. Givosiran is proposed as a 2.5 mg/kg once monthly dose administered by subcutaneous (SC) injection, which is available in a single-dose 189 mg/ml vial. Givosiran is not currently approved in any jurisdiction.

Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinic acid synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference. This results in reduction liver ALAS1 mRNA levels and thereby decreases neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG). ALA and PBG are considered as the key factors of attacks and other manifestations of AHP. Givosiran may prevent or reduce the manifestations of severe and life-threatening attacks of AHP by reducing accumulation of neurotoxic ALA and PBG.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212194 relevant to this review:

- 08/29/2016: Orphan drug designation for the treatment of AHP granted.
- 05/23/2017: Breakthrough therapy designation granted.
- 06/05/2019: NDA 212194 submission for the treatment of AHP received.
- 09/11/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for givosiran.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Porphyrias are caused by enzyme defects of heme biosynthesis.¹ They are categorized into acute and non-acute as well as hepatic and erythropoietic porphyrias. Acute hepatic porphyrias (AHP) contains 4 subtypes: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and delta-aminolevulinic acid dehydratase deficiency porphyria (ADP), each resulting from a genetic defect leading to deficiency in one of the enzymes of the heme synthesis pathway in the liver. These defects cause accumulation of the neurotoxic heme intermediates, ALA and PBG. Common symptoms of AHP include abdominal pain, weakness, nausea, and fatigue. AHP may manifest as acute attacks that produce serious abdominal, psychiatric, neurological, or cardiovascular symptoms. The intermittent attacks are sometimes life-threatening^a due to neurologic complications, such as seizures and paralysis.²

AHP are genetic disorders that are rare and may be difficult to diagnose. It is estimated that about 1 in 10,000 Europeans have a mutation in one of the genes that cause AIP, VP or HCP^b. These mutations have been found in all ethnic and racial groups.³ The majority (80-90%) of confirmed genetic carriers remain asymptomatic, and others may have one or a few acute attacks throughout life.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The initial management of AHP is focused on eliminating factors that may be contributing to an attack, including inducer medications, caloric deprivation, and dehydration.⁴ The American Porphyria Foundation (APF) and the European Porphyria Network (EPNET) maintain drug lists that are safe or hazardous. Administration of intravenous (IV) calories and fluid may stop the attack for some patients. Opiates are often needed, sometimes in large doses, to relieve pain.⁴

^a Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

Panhematin (hemin for injection (IV heme)) is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate. It is the only available therapy for an acute attack. IV hemin is not approved as a chronic treatment to prevent attacks. IV hemin is a human blood-derived heme formulation. IV hemin was first used in the early 1970s and has been approved by the FDA since 1983 for the indication stated as above. Infusion site phlebitis has been seen in about 4% of infusion of IV hemin. The risk of phlebitis may be minimized by use of a large arm vein or a central venous catheter. Other warnings and precautions are elevated iron and serum ferritin, transient and mild anticoagulant effects, reversible renal shutdown, and risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (JCD) agents.⁵

4 Benefit Assessment

The efficacy of givosiran in patients with AHP was evaluated in the ENVISION trial (NCT 03338816). ENVISION trial was a reandomized, double-blind, placebo-controlled, multinational study.⁶ There were 94 patients enrolled in the ENVISION trial, including 89 patients with AIP, 2 patients with VP, 1 patient with HCP, and 2 patients with no identified mutation. Patients were randomized 1:1 to receive once monthly SC injection of givosiran 2.5 mg/kg or placebo during 6-month period. The inclusion criteria included a minimum of 2 porphyria attacks requiring hospitalization, an urgent healthcare visit, or IV hemin therapy at home in the 6 months prior to enrollment. During the study, IV hemin use was permitted for the treatment of acute porphyria attacks. The median age of patients was 38 years (19-65 years), 89% of patients were females and 78% were white. Efficacy in the 6-month period was measured by the rate of porphyria attacks that required hospitalization, an urgent healthcare visit, or IV hemin therapy at home. Table 1 provides efficacy results for givosiran. Patients with AHP experienced an average of 70% [95% confidence interval (CI): 60%, 80%] fewer porphyria attacks compared to placebo.

Table 1: Rate of porphyria attacks and days of Hemin use in patients with AHP over the 6-month double-blind period of ENVISION trial

	Givosiran N=48	Placebo N=46
Mean rate (95% CI) of porphyria attacks	1.9 (1.3, 2.8)	6.5 (4.5, 9.3)
Mean days (95% CI) of Hemin use	4.7 (2.8, 7.9)	12.8 (7.6, 21.4)

Patients in the givosiran arm had a reduction use of IV hemin, urinary ALA, and urinary PBG compared to those in placebo arm. Patients treated with givosiran had fewer days of opioid and non-opioid analgesic use than those on placebo.

The medical officer concluded in the mid-cycle presentation that there was a substantial improvement on clinically significant endpoints,^c “decreased annualized frequency of attacks relative to baseline – givosiren 68%; placebo 10%.”⁷

5 Risk Assessment & Safe-Use Conditions

In the ENVISION trial, there were 48 patients who received 2.5 mg/kg givosiran and 46 patients who received placebo, administered once monthly via SC injection. The median duration of therapy was 5.5 months (range 2.7-6.2 months) with 47 patients who received at least 5 months of therapy. There were no deaths reported during the trial.

The following adverse reactions^d were reported during the trial.

5.1 ANAPHYLACTIC REACTION

There were anaphylaxis reactions reported in the clinical trial that occurred in less than 1% of patients. In the prescribing information, Section 2.2 Dosage and Administration states that givosiran is intended for subcutaneous use only by a healthcare professional. In Section 5 Warnings and Precautions, healthcare providers are advised to make sure that medical support is available to manage anaphylactic reactions. Healthcare providers are to monitor signs and symptoms of anaphylaxis, and to immediately discontinue givosiran therapy if anaphylaxis occurs and manage the reaction appropriately.

5.2 HEPATIC TOXICITY

In the ENVISION trial, 15% of patients treated with givosiran was observed with transaminase (ALT) elevations of at least 3 times the upper limit of normal (ULN). ALT elevations were reported primarily between 3-5 months following therapy. Healthcare providers are advised to monitor liver function tests before givosiran therapy, every month during the first 6 months, and as clinically indicated afterwards. For severe or clinically significant ALT elevations, Healthcare providers are to interrupt or discontinue the therapy. In Section 2.1 Dosage and Administration, there are instructions on how to resume therapy after therapy interruption.

5.3 RENAL TOXICITY

Fifteen percent of patients in the givosiran arm was reported to have a renal-related adverse reaction. Renal adverse reactions included elevated serum creatinine levels and decreased estimated glomerular filtration rate. At month 3, the median increase in serum creatinine was 0.07 mg/dL. In the prescribing

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

information, Healthcare providers are advised to monitor renal function during the treatment with givosiran if clinically indicated.

5.4 INJECTION SITE REACTIONS

In the ENVISION trial, 25% of patients who received givosiran was reported to have injection site reactions, including erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. These reactions were mild (92% of patients) or moderate (8% of patients). One patient was observed to have a single, transient, recall reaction of erythema at a prior injection site.

6 Expected Postmarket Use

If givosiran is approved, it is expected to be prescribed by healthcare providers who are familiar with managing AHP such as gastroenterologists, hematologists, neurologists and administered by a nurse in either a hospital setting or outside a hospital setting, such as at the patient's home.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for givosiran beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of givosiran on the basis of the efficacy and safety information that is currently available.⁶

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for givosiran, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, the expected duration of treatment, and seriousness of known or potential adverse events.

AHP are genetic disorders that are very rare and may be very difficult to diagnose. It is estimated that about 1 in 10,000 Europeans have a mutation in one of the genes that cause AIP, VP or HCP. Common symptoms of AHP include abdominal pain, weakness, nausea, and fatigue. AHP may manifest as acute attacks that produce serious abdominal, psychiatric, neurological, or cardiovascular symptoms. The intermittent attacks are sometimes life-threatening due to neurologic complications, such as seizures and paralysis.

IV hemin is the only current available therapy for an acute attack. It is not approved as a chronic treatment to prevent attacks. There is an unmet need for a maintenance therapy to prevent recurrent AHP attacks.

In the ENVISION trial, givosiran decreased the annualized frequency of attacks relative to baseline – givosiran 68% versus placebo 10%. This trial demonstrated substantial improvement on clinical endpoints. If givosiran is approved, it is expected to be prescribed by healthcare providers who are

familiar with managing AHP such as gastroenterologists, hematologists, neurologists and administered by a healthcare professional in either a hospital setting or outside a hospital setting, such as at the patient's home. The concerned risks associated with the use of givosiran are anaphylactic reactions, liver toxicity, renal toxicity, and injection site reactions. These risks will be communicated in the prescribing information section 2 Dosage and Administration, as well as section 5 Warnings and Precautions. Healthcare professionals who are likely to prescribe givosiran are expected to be familiar with the risks and management of anaphylactic reaction, hepatic/renal toxicities, and injection site reactions.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for givosiran to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ Stolzel, U. Doss, MF., and Schuppan, D Clinical Guide and update on Porphyria, Gastroenterology, available online 05/11/2019, <https://www.sciencedirect.com/science/article/pii/S0016508519408834?via%3Dihub>

² Sood, GK and Anderson, KE Acute Intermittent Porphyria: Management, www.UpToDate.com, accessed 07/09/2019

³ <https://porphyriafoundation.org/patients/about-porphyria>, accessed 09/24/2019

⁴ Acute hepatic porphyria, Bissell, DM and Wang, B Journal of Clinical and Translational Hepatology. 2015 Mar; 3(1): 17-26.

⁵ "Hemin for injection" prescribing information, 07/2017

⁶ Givosiran draft prescribing information, 10/15/2019

⁷ Dmytrijuk, A and Robie-Suh, K Givosiran NDA 212194 mid-cycle presentation, 09/03/2019

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