CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217171Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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
Application Number	217171
PDUFA Goal Date	February 26, 2023
OSE RCM #	2022-1028
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation:	Laura Zendel, Pharm.D., BCPS
Review Completion Date	February 17, 2023
Subject	Evaluation of Need for a REMS
Established Name	pegcetacoplan injection
Trade Name	Syfovre
Name of Applicant	Apellis Pharmaceuticals, Inc.
Therapeutic Class	complement inhibitor
Formulation(s)	150 mg/mL vial
Dosing Regimen	pegcetacoplan 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days

This memo by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the 505(b)(1) submission Syfovre (pegcetacoplan injection) is necessary to ensure the benefits outweigh its risks.

On May 26, 2022, Apellis Pharmaceuticals, Inc. (the Applicant) submitted a New Drug Application (NDA) 217171 for pegcetacoplan with the proposed indication for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).[1,2] On November 17, 2022, a major amendment letter was sent to the Applicant with the PDUFA goal date extended by 3 months to February 26, 2023, due to a major amendment regarding submission of 24 month safety and efficacy data. This application is under review in the Division of Ophthalmology (DO). The applicant did not submit a proposed REMS or a risk management plan with this application.

Syfovre (pegcetacoplan injection) is a complement inhibitor and is a 505(b)(1) submission, non-new molecular entity. Empaveli (pegcetacoplan) NDA 215014 was originally approved by the FDA on May 14, 2021 for the subcutaneous treatment of adult patients with paroxysmal nocturnal hemoglobinuria.[3,4] Empaveli was approved with a REMS to ensure the benefits of the drug outweigh the risk of serious and life threatening infections caused by encapsulated bacteria.[4] Syfovre (pegcetacoplan injection) is supplied as a 150 mg/mL vial. The proposed dosing regimen is pegcetacoplan injection 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days. Syfovre is not currently approved in any jurisdiction.

The efficacy of pegcetacoplan in patients with GA secondary to AMD was demonstrated in two Phase 3 studies: Study APL2-304 (NCT 03525613) and Study APL2-303 (NCT 03525600).[2] The two studies were similar in design: multicenter, double-masked, randomized, parallel-group, sham-controlled studies. The FDA clinical reviewer concluded that the studies indicated that pegcetacoplan was effective for the treatment of GA secondary to AMD.[2,5]

The safety of pegcetacoplan was evaluated in two Phase 3 clinical trials in patients with GA secondary to AMD, Study APL2-304 (NCT 03525613) and Study APL2-303 (NCT 03525600).[2] In the combined safety population from Study APL2-304 and Study APL2-303, 839 patients received pegcetacoplan and 417 patients received sham. Common adverse reactions reported with pegcetacoplan included ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage. The serious risks associated with pegcetacoplan include endophthalmitis and retinal detachments, neovascular AMD, intraocular inflammation, and increased intraocular pressure. If approved, these serious risks will be communicated in the warnings and precautions section of the label.

The FDA clinical pharmacology reviewer indicated that there is low systemic exposure of pegcetacoplan observed following intravitreal administration of 15 mg doses either monthly or every two months.[6] The DRM and DO agree that a REMS is not necessary to ensure the benefits of Syfovre (pegcetacoplan injection) outweigh the risks for the treatment of GA secondary to AMD. As there is low systemic absorption with intravitreal administration, Syfovre does not have the same risk of serious infections caused by encapsulated bacteria associated with the approved subcutaneous formulation of pegcetacoplan.[7] As such, the intravitreal formulation of pegcetacoplan does not have the same benefit

risk profile of the subcutaneous formulation of pegcetacoplan, which required a REMS for the risk of serious and life-threatening infections caused by encapsulated bacteria. The likely prescribers will be ophthalmologists who should have experience managing the serious adverse events reported with Syfovre (pegcetacoplan injection).

REFERENCES

[1] Proposed prescribing information for pegcetacoplan as currently edited by FDA, last accessed February 17, 2023.

[2] Pegcetacoplan NDA 217171 Statistical Review and Evaluation. October 24, 2022.

[3] Empaveli (pegcetacoplan) package insert. Waltham, MA: Apellis Pharmaceuticals, Inc., 2021 May.

[4] NDA approval letter for Empaveli (pegcetacoplan) NDA 215014, May 14, 2021.

[5] Pegcetacoplan NDA 217171 Statistical Review and Evaluation addendum. January 12, 2023.

[6] Zhang D, Bi Y, Ji P, Doddapaneni S. Pegcetacoplan NDA 217171 Office of Clinical Pharmacology Review. October 26, 2022.

[7] Boyd W. Division of Ophthalmology (DO). Pegcetacoplan NDA 217171. Electronic communication. November 1, 2022.

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/s/

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