CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217171Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 16, 2023

To: Diana Willard, CPMS
Office of Regulatory Operations, Division of Regulatory Operations for Specialty Medicine

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for SYFOVRE™ (pegcetacoplan injection), for intravitreal use

NDA: 217171

Background:
In response to the Division of Regulatory Operations for Specialty Medicine (DROSM) consult request dated June 27, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for SYFOVRE™ (pegcetacoplan injection), for intravitreal use.

Labeling: OPDP has reviewed the attached proposed PI emailed to OPDP on February 13, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on February 13, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 301-796-1233 or carrie.newcomer@fda.hhs.gov.

22 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

CARRIE A NEWCOMER
02/16/2023 10:47:34 AM

MEMORANDUM

ADDENDUM TO LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 12, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217171
Product Name and Strength:	Syfovre (pegcetacoplan) injection, 15 mg/0.1 mL
Applicant/Sponsor Name:	Appelis Pharmaceuticals, Inc.
OSE RCM #:	2022-1030-1
TTT ID #:	2022-2214
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS.
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 PURPOSE OF MEMORANDUM

On November 15, 2022, the Applicant submitted 24-month safety and efficacy data from the Phase 3 APL2-303 (DERBY) and APL2-304 (OAKS) studies which constitutes a major amendment. Within the submission, the Applicant also submitted new container label, carton labeling and Prescribing Information (PI) for Syfovre (Appendix A) to replace those submitted as part of the initial NDA submission on May 26, 2022. Thus, this memorandum captures our review of the new container label, carton labeling, and PI received on November 15, 2022.

2 DISCUSSION

On August 24, 2022, we completed our review of the container label, carton labeling, and PI received on May 26, 2022 under OSE RCM# 2022-1030.[a] We compared the new container label, carton labeling, and PI received on November 15, 2022 with the previous labels and labeling to determine if our previous recommendations under OSE RCM #2022-1030 are applicable to the new labels and labeling, as well as to determine if the new labels and labeling are acceptable from a medication error perspective.

[a] Getahun, S. Label and Labeling Review for Syfovre (NDA 217171). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 24. OSE RCM No.: 2022-1030.

We note the Applicant has implemented changes throughout Section 2. For example, the frequency within the recommended dosage has been revised [redacted] to [redacted]" Additionally, Step 4 within the *Preparation for Administration* instructions (Section 2.3) has been revised; however, we did not identify concerns with the proposed revisions from a medication error perspective.

In Section 16, we note the Applicant has removed [redacted] which we find acceptable. Thus, our previous recommendation for the PI is not applicable to the new PI received on November 15, 2022. We additionally note, the same revision has been applied to the carton labeling to remove [redacted] from the "Carton Contents" on the side panel. Thus, one of our previous recommendations for the carton labeling is not applicable to the new carton labeling received on November 15, 2022.

3 CONCLUSION

We have no recommendations for the current proposed PI; however, the container labels and carton labeling received on November 15, 2022 can be improved from a medication error perspective. We provide our identified medication error issues, our rational for concern and our proposed recommendation to minimize the risk of medication error in section 4 for Appelis Pharmaceuticals, Inc.

4 RECOMMENDATIONS FOR APPELIS PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Appelis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	Discard statement is not included on the container label.	Including an appropriate discard statement will facilitate proper handling of the product.	We recommend including the discard statement "discard unused portion" immediately following or in close proximity to the package type term, if space permits. For example: "Singe-dose vial – Discard unused portion"
2.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree

Table 1. Identified Issues and Recommendations for Appelis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	first numeric degree measurement in the temperature ranges.		measurement of temperature ranges. For example: "2°C - 8°C (36°F - 46°F)".
3.	As currently presented, we note that the container label is missing the name of manufacturer, packer, or distributor of the drug.	Per 21 CFR 201.10(i), small labels are required to include, at a minimum the: • Proprietary name • Established name • Product strength • Identifying lot or control number • Name of manufacturer packer, or distributor of the drug Additionally, USP requires the label of an official drug product bear an expiration date.	Revise the container label to include the name of manufacturer, packer, or distributor of the drug per 21 CFR 201.10(i). Consider removing the "Administration: see package insert" statement on the container label to ensure sufficient space is available for the minimally required product information.
4.	As currently presented, the route of administration is not included on the principal display panel (PDP).	The route of administration statement is considered to be "critical information" that should appear on the PDP to avoid medication errors involving wrong route of administration. For more information see Guidance for industry *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors."*[b]	Add the route of administration statement "For Intravitreal Use" on the PDP, if space permits.

[b] Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Table 1. Identified Issues and Recommendations for Appelis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
5.	As currently presented, the (b) (4) statement can be improved.	The terminology (b) (4) (b) (4) is not consistent with the terminology used to describe current labeling (i.e., prescribing information).	Revise the (b) (4) statement (b) (4) (b) (4) (b) (4) to read "Dosage and Administration: See Prescribing Information."
6.	The statement (b) (4) (b) (4) is included in the bulleted list of carton contents on the back panel.	The terminology (b) (4) (b) (4) is not consistent with the terminology used to describe current labeling (i.e., Prescribing Information).	Revise the statement (b) (4) (b) (4) to "One Prescribing Information."
7.	The net quantity statement does not appear on the PDP.	Per *Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors*[c] the net quantity statement should appear on the PDP.	We recommend that the net quantity statement appear on the principal display panel (PDP) but separated from and less prominent than the statement of strength and strength (e.g., not highlighted, boxed, or bolded). You may consider incorporating the net quantity into the package type statement on the PDP. For example: "One single-dose vial – Discard Unused Portion"

[c] Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 15, 2022

Prescribing Information (Image not shown)

Prescribing Information, available from: \\CDSESUB1\EVSPROD\nda217171\0019\m1\us\draft-annot-labeling-text.pdf

Container label

Carton labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOFANIT N GETAHUN
01/12/2023 10:31:10 AM

VALERIE S VAUGHAN
01/12/2023 12:03:26 PM

Clinical Inspection Summary Addendum

Date	November 08, 2022
From	Roy Blay, Ph.D. Michele Fedowitz, M.D., Acting Team Lead Jenn Sellers, M.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Martin Nevitt, M.D., Reviewing M.O. Jennifer Harris, M.D., Team Leader William Boyd, M.D., Supervisory M.O. Milalynn Victorino, P.M. Division of Ophthalmology
NDA	217171
Applicant	Apellis Pharmaceuticals, Inc.
Drug	Syfovre (pegcetacoplan ophthalmic solution, intravitreal) injection
NME	No
Therapeutic Classification	Anti-complement therapy
Proposed Indication(s)	Treatment of geographic atrophy secondary to age-related macular degeneration
Consultation Request Date	23 Jun 22
Summary Goal Date	19 Oct 22
Summary Uploaded into DARRTS	14 Oct 22
Action Goal Date	26 Oct 22
PDUFA Date	26 Nov 22

This is an addendum to the Clinical Inspection Summary uploaded to DARRTS on 14 Oct 22 to provide OSI input on its review of a sponsor's response received on 21 Oct 22 to an 18 Oct 22 Information Request (IR) sent by FDA. The IR requested clarification of adverse event (AE) reporting and relevant data cutoff dates stemming from the inspection of the clinical site of Dr. Lally.

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Some of the clinical site inspections noted what appeared to be unreported AEs. FDA sent an IR requesting that the sponsor address any unreported AEs by clinical site, severity, dates of occurrence, actions taken with the study treatment, outcome, causality, reason(s) why the unreported AE was not reported, and relevant data cutoff dates.

Review of the sponsor's response to the IR concludes that perceived inconsistencies in AE reporting appeared attributable to the sequential reporting of AEs in multiple reports and the result of timing as to when subjects reported their AEs to the site and/or the timing of the sites in entering the AEs into the EDC system. Overall, AE reporting for this application appears adequate.

II. BACKGROUND

During the inspection of Dr. Lally's site, not all AEs reported in the source data appeared to be in the data listings. To address the potential of unreported AEs, OSI issued an IR to the sponsor on 18 Oct 22 requesting specific details regarding AE reporting.

The sponsor responded to the IR on 21 Oct 22. The response consisted of a cover letter and a five-page response including a tabular presentation of the AE reporting that took place for Studies APL2-303 and APL2-304, the associated data cutoff dates, and the scope of reporting for each study report and a dataset reference.

III. RESULTS:

Per the sponsor's response, subjects reported their AEs to the site and the sites then entered the AEs into the Electronic Data Capture (EDC) system. The data entry into the EDC may have lagged the AE reporting. In addition, both Studies APL2-303 and APL2-304 had ongoing safety follow up and safety reporting done in a sequential manner with 12-month, 18-month, and 24-month updates, as well as a 120-day Safety Report to the NDA submission. Because of the data entry lag and the sequential updates to the safety database, there may have appeared to have been unreported AEs; however, they were eventually reported. For example, changes in AE data reporting within a given dataset (e.g., the Month 12 dataset) were included in the Post-12 Month reports. Similarly, any changes in the Month 18 dataset were then included in the 120-Day Safety Update. Thus, any changes in AE reporting were captured in the subsequent dataset until all AEs through Month 24 were reported.

The sponsor compared AE reporting between the submission and the 120-Day Safety Update. Overall, they noted a small percentage of AEs not reported in the initial NDA submission but reported in the 120-Day Safety Report. None were serious per the sponsor. All AEs for both studies were included in the 120-Day Safety Report other than a single case of low glomerular filtration (Subject (b) (6) in Study APL2-303), identified after the 120-Day Safety Report and to be included in the Study APL2-303 24-Month CSR submission.

Reviewer's comments: Review of the sponsor's response to the IR indicates that AE reporting appears to have been adequate. The perceived unreported AEs were due to the sequential AE reporting as well as minor lags in AE reports being entered into the EDC.

Except for a single AE (Subject [redacted] (b) (6), low glomerular filtration), which will be reported in the next update, all AEs are accounted.

{See appended electronic signature page}

Michele Fedowitz, M.D. on behalf of
Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Acting Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
DO/Division Director/Wiley Chambers
DO/Supervisory MO/William Boyd
DO/MO/ Medical Team Leader/Jennifer Harris
DO/Reviewing MO/Martin Nevitt
DO/Project Manager/Milalynn Victorino
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Acting Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/GCPAB/Program Analyst/Yolanda Patague

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/s/

MICHELE B FEDOWITZ
11/08/2022 08:06:01 AM

JENN W SELLERS
11/08/2022 09:36:20 AM

Clinical Inspection Summary

Date	October 14, 2022
From	Roy Blay, Ph.D. Karen Bleich, M.D., Team Lead Jenn Sellers, M.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Martin Nevitt, M.D., Reviewing M.O. Jennifer Harris, M.D., Team Leader William Boyd, M.D., Supervisory M.O. Milalynn Victorino, P.M. Division of Ophthalmology
NDA	217171
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NME	No
Therapeutic Classification	Anti-complement therapy
Proposed Indication(s)	Treatment of geographic atrophy secondary to age-related macular degeneration
Consultation Request Date	23 Jun 22
Summary Goal Date	19 Oct 22
Action Goal Date	26 Oct 22
PDUFA Date	26 Nov 22

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators, Drs. Fineman, Wykoff, Lally, and Chiang were inspected in support of this NDA. The primary efficacy data were requested from the sites of Drs. Fineman, Wykoff, and Chiang and provided by the sponsor. These data were compared with the line listings and no discrepancies were noted. However, because these primary efficacy data provided by the sponsor were not certified copies of the original data, the integrity of these data could not be evaluated.

In assessing the reliability of safety data, the inspections of Drs. Lally and Chiang revealed a number of adverse events (AEs) that appear to have been reported by these CIs but not by the sponsor. We recommend that the review division include any unreported AEs in its evaluation of the safety data. We also recommend that the review division forward an information request to the sponsor asking that the sponsor audit the safety data and report all AEs that were not included in this NDA.

Otherwise, based on the results of these inspections, Protocols APL-303 and 304 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Syfovre in the treatment of geographic atrophy secondary to age-related macular degeneration

Inspections were requested for the following protocols in support of this application:

Protocol APL2-303 is entitled, "A 24-Month Phase III, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD)

Protocol APL2-304 is entitled, "A Phase III, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD)

Reviewer Note: The protocols are essentially identical other than mesopic microperimetry being performed for Protocol APL2-304.

The investigational product was Syfovre, a complement inhibitor, for intravitreal injection. Syfovre binds to complement C3 and broadly inhibits the complement cascade, which is involved in multiple inflammatory processes, possibly including those related to the development of GA secondary to AMD.

The studies were Phase 3 multi-center, randomized, double-masked, sham-controlled, clinical studies to evaluate the efficacy of Syfovre as compared to sham injection in the treatment of GA secondary to AMD.

The primary objective was to evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD as assessed by the change in the total area of GA lesions from baseline as measured by fundus autofluorescence (FAF).

The primary efficacy endpoint was the change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.

For Protocol APL2-303, 621 subjects were assigned to randomly selected treatment across 122 domestic and foreign sites. The four treatment groups were pegcetacoplan (15 mg/0.1.mL) monthly (PM), the same dosage of pegcetacoplan every other month (PEOM), and to maintain blinding, sham injection treatment monthly (SM) or every other month (SEOM). Subjects were randomized 2:2:1:1 using a web-based randomization system to receive treatment with PM, PEOM, SM or SEOM, respectively. The randomization scheme was maintained by the Sponsor, or designee. Subject randomization was stratified by GA lesion area at screening based on assessment from the reading center ($< 7.5\ mm^2$, $\geq 7.5\ mm^2$) and presence of CNV in the fellow eye (yes; no).

The first subject was screened on (b) (6), with the first subject enrolled on (b) (6), the last subject completing on (b) (6) and the data lock for the Month 12 analysis on 12 Aug 21. For Protocol APL2-303a, the last subject completed the Month 18 Visit on (b) (6) with the data lock for the Month 18 analysis on 16 Feb 22.

For Protocol APL-304, 637 subjects were assigned to randomly selected treatment across 110 domestic and foreign sites. The first subject was screened on (b) (6), with the first subject enrolled on (b) (6), the last subject completing on (b) (6), and the data lock for the Month 12 analysis on 18 Aug 21. For Protocol APL2-304a, the last subject completed the Month 18 Visit on (b) (6) with the data lock for the Month 18 analysis on 18 Feb 22.

The sites for inspection were chosen in collaboration with the reviewing division and were selected based primarily on relatively large study subject enrollment and no history of prior inspection.

III. Results:

1. Mitchell Fineman, MD
   Mid Atlantic Retina - Huntingdon
   Valley Mid Atlantic Retina
   727 Welsh Road Suite 206
   Huntingdon Valley, PA. 19006-6398

   Site: 01-058
   Protocol: APL2-303
   Inspection Dates: 9-16 Aug 2022

   At this site, 45 subjects were screened, 23 subjects were enrolled, and 17 subjects completed the study. The site was responsible for conducting timely optical imaging and submitting those photographs to the central reading site (b) (4) (b) (4) who then determined the primary efficacy endpoint via FAF. Review of

email correspondence confirmed submission and receipt of the photographs between (b) (4) and the site. The primary efficacy data as determined by (b) (4) was not provided to the clinical site.

Study records reviewed included subject eligibility, randomization, adverse events, concomitant medications, investigational product (IP) administration records and study progress notes.

Protocol deviations included the use of IP subjected to temperature excursions. The IP was to be stored at 2-8° C while intermittent temperature excursions were observed between 8.1 and 9° C. The sponsor declared multiple kits as Not Fit for Use (NFFU) based on kits that either experienced temperature excursions or for which temperatures during transportation were unknown. Some of these kits were administered to subjects as it was unknown to the investigator at the time that they had been declared NFFU. Subsequent follow up of these subjects revealed no safety issues. In addition, subsequent sponsor investigation demonstrated that the IP remained suitable for use at temperatures of 25° C for seven days and up to three freeze-thaw cycles. As the IP kits were unlikely to have been subjected to conditions exceeding these conditions, the efficacy of the IP would appear to have remained unaffected. These temperature deviations were also addressed in Memos-to-File, e-mail and telephone communications between the clinical site and the sponsor, and a Corrective and Preventive Action Report.

> *Reviewer's Note: In personal communications with the Division Director, Division of Ophthalmology, he stated that he would not be concerned with temperature excursions to 10°C for this product.*

Other study records reviewed included informed consent, financial disclosure, site training records, delegation of duties, investigational product (IP) control, concomitant medications, and sponsor monitor, and IRB correspondence.

Overall, adherence to the regulations and the investigational plan appeared adequate.

2. Charles Wykoff, M.D., Ph.D.
   Retina Consultants of Texas – The Woodlands
   17350 St. Luke's Way, Ste 120
   The Woodlands, TX.

   Site: 01-057
   Protocol: APL2-303
   Inspection Dates: 22-26 Aug 2022

   At this site, 67 subjects were screened, 42 subjects failed screening with 25 subjects enrolled, randomized, and treated with the IP. There were 20 subjects completing the study with four subject withdrawals and one lost to follow up.

The informed consent process was reviewed for all 67 screened subjects. No deficiencies were noted. Review of email correspondence confirmed submission and receipt of the photographs between (b) (4) and the site.

Other study records reviewed for the 25 randomized subjects included study training records, delegation logs, laboratory qualifications, the enrollment log, case report forms, electronic records, IP temperature logs drug accountability logs, and IRB, sponsor and monitor correspondence. Subject records reviewed for the 25 randomized subjects included medical histories, concomitant medications, adverse events, laboratory reports, questionnaires and visit assessments.

Overall, adherence to the regulations and the investigational plan appeared adequate.

3. David R. Lally MD
   Retina Research Institute at New
   England Retina Consultants, PC
   3640 Main Street Suite 201 + 202 A
   Springfield, MA 01107-1139

   Site: 01-530
   Protocol: APL2-304
   Inspection Dates: 1-5 Aug 2022

   At this site, 45 subjects were screened, 29 subjects were randomized to the study, four subjects discontinued, and 25 subjects completed the study. The informed consent forms for all randomized subjects were reviewed. The inspection confirmed the acquisition and submission of the fundus autofluorescence (FAF) images to the central reader site for determination of the primary efficacy endpoint.

   Study records reviewed included training records, electronic records systems, masked IP accountability records financial disclosure, and sponsor monitor, and IRB correspondence. Protocol deviations included the failure to collect anti-APL2 blood samples for subjects not consenting to genetic testing (a misunderstanding by the study coordinator) or re-consenting subjects with ICF v4.0 resulting from a change to the 24-hour contact number. Monitors conducting the first four monitoring visits did not identify these protocol deviations as such.

   AEs in the source documents were compared against an Excel spreadsheet obtained at the site from (b) (4) which listed all AEs reported in the Electronic Data Capture (EDC). AEs in the source documents were consistent with the Excel spreadsheet; however, not all AEs reported in the EDC were in the line listings in the submission as shown in the table below.

Subject/ Randomization Arm	Date	Adverse Event (in EDC, not line listings in the submission)
(b) (6) / Pegcetacoplan monthly	(b) (6)	Acute kidney injury
		Dementia
		Worsening Anxiety
		Microscopic hematuria
		Microalbuminuria 2/2 acute kidney injury
		Leukocytosis from stress
		Head Strike
		Insomnia
		Cardiogenic Syncope
		Delirium
		Delusions
		Cracked tooth
		Stomach Cramps
(b) (6) /Sham every other month		Broken Right Pinky Toe
(b) (6) / Pegcetacoplan every other month		Worsening right knee pain
(b) (6) /Sham monthly		Covid 19
(b) (6) Pegcetacoplan monthly		Candidal vulvovaginitis
		Right big toe infection
(b) (6) Pegcetacoplan monthly		Worsening hip pain
		Fall
		Atrial; tachycardia
		Pain left leg
		Chest pain-non cardiac
		Gluteus medius torn tendon
(b) (6) Pegcetacoplan every other month		Worsening eczema both hands
		Retinal hemorrhage
(b) (6) Sham monthly		Hypotension
		Worsening hyperlipidemia
		Decreased visual acuity

	(b) (6)	Worsening dry eye (OD)
		Worsening dry eye (OS)
(b) (6) /Sham every other month		Seasonal allergies
		Eosinophilia
		Generalized back pain
(b) (6) /Sham every other month		Fractured Left Wrist
		Worsening Glaucoma (OS)
		Pain post carpal tunnel surgery
		Worsening wet macular degeneration
		Carpal tunnel Right hand
		A Fib
		Sore right arm secondary to covid vaccine
(b) (6) /Sham every other month		Upper back pain secondary to arthritis
(b) (6) Pegcetacoplan every other month		Left ankle pain
(b) (6) Pegcetacoplan monthly		Worsening Waldenstrom's disease
(b) (6) Pegcetacoplan every other month		Right leg pain secondary to arthritis
		Acute anal hemorrhoid
		Worsening bronchial asthma
(b) (6) /Sham every other month		Epistaxis
(b) (6) /Sham every other month		Common cold
		Controlled A Fib
(b) (6) / Pegcetacoplan monthly		Hypotension
(b) (6) Sham monthly		Cracked upper tooth
		Worsening cataract (OD)
		Worsening cataract (OS)
(b) (6) / Pegcetacoplan monthly		Wet macular degeneration related to CNV (OD)

(b) (6) /Sham monthly	(b) (6)	Seasonal Allergies
		Worsening cataract (OD)
		Worsening cataract (OS)
		Skin rash on neck
(b) (6) Sham monthly		Facial dermatitis
		Upper lip dermatitis
		Allergic rash on back
		Decreased visual acuity (OD)
		Decreased visual acuity (OS)
		Fall
		Bruised forehead
(b) (6) / Pegcetacoplan monthly		Decrease visual acuity 10 letters (OS)
		Geographic atrophy progression
		Vasovagal syncope
		Fractured nose
		Cracked tooth
		Facial bruising from fall
		Fall NA
		Eyelid ecchymosis (OD)
		Eyelid ecchymosis (OS)
(b) (6) Pegcetacoplan every other month		Cellulitis right shin

Review of the labeling indicates that adverse events are essentially limited to a variety of ophthalmic complications; therefore, the Division may wish to assess the reported non-ophthalmic adverse events for potential significance.

Overall, adherence to the regulations and the investigational plan appeared adequate.

4. Allen Chiang, MD
   Mid Atlantic Retina - Bethlehem
   5325 Northgate Drive Suite 103
   Bethlehem, PA 18017-9411
   Mid Atlantic Retina – Bethlehem
   727 Welsh Rd Ste 206
   Huntingdon Valley, PA 19006-6398

   Site: 01-530
   Protocol: APL2-304
   Inspection Dates: 24-31 Aug 2022

At this site, 41 subjects were screened, 23 subjects failed screening,18 subjects were enrolled, and 15 subjects completed the study. Subject records reviewed included informed consent forms, eCRFs, concomitant medication logs, and test article accountability. I reviewed copies of the adverse event logs as provided by the ORA investigator. The adverse events listed below do not appear to have been reported in the line listings by the sponsor. As recommended in Section I above, an information request to the sponsor may address these omissions.

Subject ID	Adverse Event (Site Log)	Start Date
(b) (6)	Anxiety	(b) (6)
	Hyperlipidemia	
	Pulmonary granuloma	
	Memory Loss	
	Hernia (hiatal)	
	Bilateral ft cramps	
	Neck Lump benign	
	Retinal Hemorrhage	
	Peripheral subretinal hemorrhage	
	Rapid Weight loss	
	Constipation	
	Rash under Breasts	
	Anemia	
	Post Fluorescein dye vomiting	
	GERD	
	Depression	
	Sleep Apnea	
	Restless leg syndrome	
	PCO OS	

Other study records reviewed included financial disclosure, protocol deviation logs, IP temperature logs, SOPs, and sponsor, monitor, and IRB correspondence.

Protocol deviations included reports of temperature excursions. Review of the submitted temperature logs revealed a single temperature excursion greater than 10° C which was 13.03° C on 15 Jan 2020. The kits affected by this temperature excursion were approved for use. As previously noted, communication with the Division of Ophthalmology indicated that there were no concerns with temperature excursions of up to 10° C and stability data submitted by the sponsor demonstrated integrity of the IP over a wide temperature range exceeding that experienced on 15 Jan 2020.

Overall, adherence to the regulations and the investigational plan appeared adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
DO/Division Director/Wiley Chambers
DO/Supervisory MO/William Boyd
DO/MO/ Medical Team Leader/Jennifer Harris
DO/Reviewing MO/Martin Nevitt
DO/Project Manager/Milalynn Victorino
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/ Acting Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Karen Bleich
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/GCPAB/Program Analyst/Yolanda Patague

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/s/

ROY A BLAY
10/14/2022 12:36:22 PM

KAREN B BLEICH
10/14/2022 04:11:56 PM

JENN W SELLERS
10/14/2022 05:10:12 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 24, 2022
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217171
Product Name and Strength:	Syfovre (pegcetacoplan) injection, 15 mg/0.1 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Apellis Pharmaceuticals, Inc.
FDA Received Date:	May 26, 2022,
OSE RCM #:	2022-1030
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS.
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 REASON FOR REVIEW

As part of the approval process for Syfovre (pegcetacoplan) injection, the Division of Ophthalmology (DO) requested that we review the proposed Syfovre prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (For Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Apellis Pharmaceuticals, Inc.

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The statement, "Each Syfovre carton (NDC 73606-020-01) contains one single-dose (b) (4) glass vial (b) (4) (b) (4)	The (b) (6) could be misinterpreted (b) (4) (b) (4)	Remove the (b) (6) (b) (6) For example, revise to, "Each Syfovre carton (NDC 73606-020-01) contains one-single dose glass vial designed to deliver 15 mg/0.1 mL solution."

5 RECOMMENDATIONS FOR APELLIS PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Apellis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	We note that the placeholder, "TRADENAME" is included on the container label and the carton labeling.	The proposed proprietary name, Syfovre, was found conditionally acceptable on July 12, 2022[a]. The proprietary name, "Syfovre," should be used	Replace the placeholder, "TRADENAME," with the conditionally acceptable proprietary name, "Syfovre."

[a] Chan, I. Proprietary Name Granted – Advice for Syfovre NDA 217171. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUL 12. RCM: 2022-1044724608.

Table 3. Identified Issues and Recommendations for Apellis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		throughout the container label and carton labeling.	
Container Label			
1.	Discard statement is not included on the container label.	Including an appropriate discard statement will facilitate proper handling of the product.	We recommend including the discard statement "discard unused portion" immediately following or in close proximity to the package type term. For example: "Singe-dose vial – Discard unused portion"
2.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example: "2°C - 8°C (36°F - 46°F)".
3.	As currently presented, we note that the container label is missing the name of manufacturer, packer, or distributor of the drug.	Per 21 CFR 201.10(i), small labels are required to include, at a minimum the: • Proprietary name • Established name • Product strength • Identifying lot or control number • Name of manufacturer packer, or distributor of the drug Additionally, USP requires the label of an official drug product bear an expiration date.	Revise the container label to include the name of manufacturer, packer, or distributor of the drug per 21 CFR 201.10(i). Consider removing the (b) (4) (b) (4) statement on the container label to ensure sufficient space is available for the minimally required product information.
4.	As currently presented, the route of	The route of administration statement is considered to	Add the route of administration statement "For

Table 3. Identified Issues and Recommendations for Apellis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	administration is not included on the principal display panel (PDP).	be "critical information" that should appear on the PDP to avoid medication errors involving wrong route of administration. For more information see Guidance for industry *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors."*[b]	Intravitreal Injection Only" without the use of abbreviation on the PDP.
Carton Labeling			
1.	As currently presented, the (b) (4) statement can be improved.	The terminology (b) (4) (b) (4) is not consistent with the terminology used to describe current labeling (i.e., prescribing information).	Revise the (b) (4) statement (b) (4) (b) (4) (b) (4) to read "Dosage and Administration: See Prescribing Information."
2.	The statement (b) (4) (b) (4) is included in the bulleted list of carton contents on the back panel.	The terminology (b) (4) (b) (4) is not consistent with the terminology used to describe current labeling (i.e., Prescribing Information).	Revise the statement (b) (4) (b) (4) to "One Prescribing Information."
3.	Under the carton contents section, the statement, (b) (4) (b) (4) (b) (4) (b) (4)	The (b) (4) could be misinterpreted (b) (4) (b) (4)	Remove the (b) (4) (b) (4) for example, "one single-dose vial of…"

[b] Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Table 3. Identified Issues and Recommendations for Apellis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The net quantity statement does not appear on the PDP.	Per *Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors*[c] the net quantity statement should appear on the PDP.	We recommend that the net quantity statement appear on the principal display panel (PDP) but separated from and less prominent than the statement of strength and strength (e.g., not highlighted, boxed, or bolded). You may consider incorporating the net quantity into the package type statement on the PDP. For example: "One single-dose vial – Discard Unused Portion"

[c] Guidance for Industry: Safety Consideration for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Syfovre that Apellis Pharmaceuticals, Inc. submitted on May 26, 2022.

Table 4. Relevant Product Information for Syfovre	
Initial Approval Date	N/A
Active Ingredient	Pegcetacoplan
Indication	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
Route of Administration	Intravitreal injection
Dosage Form	Injection
Strength	15 mg/0.1 mL (150 mg/mL)
Dose and Frequency	15 mg to each affected eye once (b) (4) (b) (4).
How Supplied	Each carton (NDC 73606-020-01) contains one single-dose 3 mL glass vial designed to deliver 15 mg/0.1 mL solution.
Storage	Refrigerate between 2°C to 8°C (36°F to 46°F). Store the vial in the original carton to protect from light.
Container Closure	Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 8, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, pegcetacoplan and NDA 217171. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Syfovre labels and labeling submitted by Apellis Pharmaceuticals, Inc..

- Container label received on May 26, 2022
- Carton labeling received on May 26, 2022
- Prescribing Information (Image not shown) received on May 26, 2022, available from
    - Annotated version: \\CDSESUB1\evsprod\nda217171\0001\m1\us\draft-annot-labeling-text.pdf
    - Clean version: \\CDSESUB1\evsprod\nda217171\0001\m1\us\draft-uspi-clean.docx

F.2 Label and Labeling Images

Container label

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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SOFANIT N GETAHUN
08/24/2022 10:12:07 AM

VALERIE S VAUGHAN
08/24/2022 10:27:01 AM