CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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:	August 4, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217225
Product Name, Dosage Form, and Strength:	Izervay (avacincaptad pegol) injection, 2 mg/0.1 mL
Applicant/Sponsor Name:	Iveric Bio, Inc.
TTT ID #:	2022-2739-1 and 2022-2742-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised trade and professional sample container labels and carton labeling received on August 3, 2023 for Izervay. The Division of Ophthalmology (DO) requested that we review the revised container labels and carton labeling for Izervay (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review,[a] and additional information request (IR)[b] sent to the Applicant.

2 DISCUSSION

In addition to our recommendations, the Division of Ophthalmology (DO) requested the Applicant revise the dosage form terminology from (b) (4) to "intravitreal solution." We note "intravitreal solution" would be a novel dosage form term that is not currently used on the market. In support of the revised dosage form terminology, DO stated that *"in the past we have labeled these products "injection, for intravitreal use/administration". Clinical proposes "intravitreal solution" to clarify that this product is in conformance with USP <789> and [to] differentiate from the particulate matter standards in USP <787> and USP <788>."* Furthermore,

[a] Getahun, S. Label and Labeling Review for Izervay (NDA 217225). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 MAR 23. TTT ID No.: 2022-2739 and 202022-2742.
[b] Puglisi, M. Information Request for Izervay. Silver Spring (MD): FDA CDER OSE (US); 2023 AUG 03. NDA 217225

DO referenced the National Cancer Institute (NCI)/Enterprise Vocabulary Service[c] definitions for "intravitreal - route of administration"[d] and "Ophthalmic solution - dosage form"[e] to support how the dosage form term "intravitreal solution" was derived.

Historically, we note that "ophthalmic solution" has been used to describe "eye drops."[f] Thus, we considered if the change in dosage form to "intravitreal solution" could result in wrong technique in administration errors. For example, we considered if users may perceive the novel dosage form term "intravitreal solution" to mean that the product may be placed or applied in or around the eye similar to how eye drops are administered as opposed to via injection as intended. We note, however, that the kit presentation with vial, filter needle, and syringe is likely to minimize wrong technique in administration error, that is, administration similar to how eye drops are administered. Additionally, we note that the appropriate route of administration "for intravitreal injection" is included on the labeling.

Therefore, we defer to our Office of Pharmaceutical Quality colleagues for the final determination on the acceptable dosage form term for the proposed product.

3 CONCLUSION

The revised trade and professional sample container labels and carton labeling received on August 3, 2023, are acceptable from a medication error perspective.

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[c] FDA's regional terminology for dosage form and route of administration is the FDA Terminology for Structured Product Labeling (FDA Terminology) which is maintained by the National Cancer Institute / Enterprise Vocabulary Service. https://www.fda.gov/industry/fda-data-standards-advisory-board/dosage-form-and-route-administration.

[d] Intravitreal Route of Administration (Code C38280). Definition: The administration of a drug within the vitreous body of the eye. https://ncithesaurus.nci.nih.gov/ncitbrowser/pages/concept_details.jsf?dictionary=NCI_Thesaurus&version=23.06d&code=C38280&ns=ncit&type=properties&key=n584363352&b=1&n=0&vse=null

[e] Ophthalmic Solution Dosage Form (Code C91163). Definition: A solution intended for administration in or around the eye. https://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&version=23.06d&ns=ncit&code=C91163&key=447140991&b=1&n=null

[f] Ophthalmic Solution Dosage Form (Code C91163). Synonyms and Abbreviations. https://ncithesaurus.nci.nih.gov/ncitbrowser/pages/concept_details.jsf?dictionary=NCI_Thesaurus&code=C91163&type=synonym

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

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

Memorandum

Date: July 20, 2023

To: Michael Puglisi, Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for IZERVAY (avacincaptad pegol) injection, for intravitreal use

NDA: 217225

Background:
In response to DROSM's consult request dated July 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for IZERVAY (avacincaptad pegol) injection, for intravitreal use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 11, 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 July 11, 2023, and our comments are provided below.

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

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Clinical Inspection Summary

Date	June 23, 2023
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Deputy Director Rhea Lloyd, M.D., Clinical Team Leader Lucious Lim, M.D., Reviewing M.O. Michael Puglisi, P.M. Division of Ophthalmology
NDA	217225
Applicant	IVERIC bio, Inc.
Drug	Izervay (avacincaptad pegol)
NME	Yes
Therapeutic Classification	Complement C5 protein inhibitor
Proposed Indication(s)	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Consultation Request Date	7 Feb 2023
Summary Goal Date	10 Jul 2023
Action Goal Date	1 Aug 2023
PDUFA Date	19 Aug 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols OPH2003 and ISEE2008 were submitted to the Agency in support of NDA 217725 for the use of Izervay in the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The clinical investigators, Drs. Cummings and Wong, as well as the sponsor, IVERIC bio, Inc., were inspected in support of this NDA.

Based on the results of these inspections, the conduct of Protocols OPJH2003 and ISEE2008, the data generated by these clinical sites, and the sponsor's oversight of these studies all appear to be adequate.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Izervay for the treatment of GA secondary to AMD. Izervay is a pegylated RNA aptamer that functions as an inhibitor of the complement C5 protein and decreases or slows down the chronic inflammation and cell death

associated with retinal aging. Reduction in inflammation may inhibit the development of GA which is the chronic progressive degeneration of the macula associated with late-stage AMD.

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

Protocol Number: OPH2003

Title: A Phase 2/3 Randomized, Double- Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-CS Aptamer) in Patients with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration

Reviewer's Note: "Zimura" was the drug name used by the sponsor during the IND phase of the application. The sponsor has since changed the name to "Izervay".

The primary objective of this randomized, double-masked, sham-controlled study was to evaluate the safety and efficacy of Izervay when administered via intravitreal (IVT) injection to subjects with GA secondary to dry AMD.

Qualifying subjects were randomized into three treatment groups in a 1:1:1 ratio to Izervay, 1 mg/eye via IVT injection, Izervay, 2 mg/eye via IVT injection, or sham injection. Subjects were treated with monthly IVT injection of Izervay and/or the sham treatment for 18 months.

The primary efficacy endpoint was the mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12.

This study was conducted at 63 clinical sites across seven countries. The first subject's first visit was 20 Jan 2016, and the last subject's last visit was on 23 Apr 2020. There were 77 subjects in Part 1 of the study and 209 subjects in Part 2 of the study.

Protocol Number: ISEE2008

Title: A Phase 3 Multicenter, Randomized, Double-Masked, Sham Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura™ (Complement C5 Inhibitor) in Patients with Geographic Atrophy

The primary objective of this Phase 3, multicenter, randomized, double-masked, sham-controlled study was to evaluate the safety and efficacy of Izervay when administered via intravitreal (IVT) injection to subjects with GA secondary to AMD.

Qualifying subjects were randomized in a 1:1 ratio to Iverzay 2 mg/eye via IVT injection or sham treatment and received monthly treatments from Day 1 to Month 11.

The primary efficacy endpoint was the mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12. The study was conducted at 205 clinical sites across 20 countries. The first subject was enrolled on 22 Jun 2020, and the last subject's last visit was on 25 Jul 2022. A total of 448 subjects were randomized in the study.

III. RESULTS

1. **Robert Wong, M.D.**
   801 West 38th Street, Suite 200
   Austin, TX

   Site: 357
   Inspection Dates: 2-4 May 2023

   Dr. Wong was inspected for the conduct of **Protocol OPH2003**. This was the first FDA inspection of Dr. Wong. At this site, 11 subjects were screened, seven were randomized, four failed screening, and six subjects completed the study.

   The primary efficacy endpoint data and adverse event reporting were verified. Other subject records reviewed included the informed consent process, the informed consent documents for all eleven subjects, physical examinations, medical histories, concomitant medications, laboratory reports, and visual examinations.

   Study related documents reviewed included IRB submissions and approvals, sponsor and monitor correspondence, electronic records, protocol deviations, investigational product (IP) accountability, training documentation, Form 1572s, delegation logs, and financial disclosure documents.

   The inspection compared the paper source records with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. **Howard Cummings, M.D.**
   Southeastern Retina Associates, PC
   161 Technology Lane
   Johnson City, TN 37604

   Site: 22
   Inspection Dates: 6-10 May 2023
   Subjects: 3

   Dr. Cummings was inspected for the conduct of **Protocol ISEE2008**. This was the first FDA inspection for Dr. Cummings. At this site, five subjects were screened, three were randomized, two failed screening, and two subjects completed the study.

The primary efficacy endpoint (GA as measured by fundus autofluorescense) was verified for the initial eligibility visit. All subsequent GA assessments were made by the vendor with the results being forward to the sponsor and not shared with the clinical site. Other subject records reviewed included informed consent forms, visual acuity (VA) and low-level visual acuity (LLVA) assessments, eligibility, concomitant medications, and spot checks of laboratory results.

Study related documents reviewed included IRB submissions and approvals, sponsor and monitor correspondence, Form 1572s, electronic records, protocol deviations, investigational product (IP) accountability, training documentation, delegation logs, and financial disclosure documents.

The inspection compared the paper source records with the data listings and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

3. IVERIC bio, Inc. (Sponsor)
8 Sylvan Way
Parsippany, NJ 07054

Protocols OPH2003 and ISEE2008
Inspection Dates: 2-11 May 2023

This was the first inspection of IVERIC bio, Inc. (IVERIC), and covered sponsor oversight of Protocols **OPH 2003 and ISEE2008**. The firm is now a wholly owned subsidiary of Astellas Pharma, Inc. IVERIC continues with its organizational structure and the development of its product applications.

The inspection included review of study documents, standard operating procedures (SOPs), data collection and handling, investigational product (IP) disposition, safety reporting and handling, selection of clinical investigators, sites, and monitors, Form FDA 1572s, financial disclosures, and data monitoring committee activities, as well as transfer of responsibilities and obligations (TOROs) to designated contract research organizations (CROs).

Senior sponsor personnel and representatives were interviewed regarding their study functions and the obligations that were transferred during the conduct of the protocols. The sponsor's processes for selecting and monitoring clinical investigators were reviewed. Monitoring plans were in place for both protocols with trained monitors conducting both on-site and remote monitoring visits and providing reports on source data verification, study deviations, and follow-up actions. The oversight of clinical investigators appeared adequate.

The sponsor responsibilities outsourced to CROs via a TORO were reviewed. CROs were interviewed regarding their study functions and the obligations that were transferred during the conduct of the protocols. The TOROs identified the specific responsibilities to be

transferred and the sponsor's oversight of the CROs was adequate. The sponsor's practices regarding data collection and handling, electronic record systems, and records retention were reviewed and appeared adequate.

The release of information on ClinicalTrials.gov by the sponsor with respect to these protocols was reviewed. Some clinical sites associated with either Protocol OPH2003 or ISEE2008 were not listed because they had not enrolled any subjects. The sponsor admitted that their omission was an oversight under previous management of clinical operations. The sponsor initialed a CAPA to update the firm's procedure CL-SOP-1031/SOP-00017, Clinical Trial Registration and Results Reporting and will update the ClinicalTrials.gov information to ensure it is accurate.

Reviewer's Note: It does not appear that this deficiency would impact safety or efficacy of the study. The sponsor's CAPA appears acceptable.

IP accountability practices were reviewed, and it was noted that the sponsor lacked an overall IP reconciliation process. The sponsor drafted a CAPA to create a written procedure for overall IP reconciliation and noted that IP reconciliation would be conducted for the ongoing protocol ISEE2008.

Reviewer's Note: Although the IP reconciliation process was not sufficient, it did not appear to have any IP accountability issues. The sponsor's CAPA appears to be acceptable.

Inspection revealed that there were some differences between source data and the final reported listings for both protocols. Further discussion with (b) (4) described the differences as being due to statistical analysis with respect to visual acuity (VA). Differences in interpretation in determining the Early Treatment of Diabetic Retinopathy Study (ETDRS) Visual Acuity Score resulted in the observed differences between source data and line listings. This lack of uniform interpretation of the Statistical Analysis Plan (SAP) was discussed with sponsor management.

Reviewer's Note: These observations would not appear to have affected safety or efficacy assessments. The statistical analysis plan was followed. The differences in Best Corrected Visual Acuity (BCVA) between source documents and data listings resulting from statistical analysis plan appeared to result in a lesser VA being reported in the line listings than that recorded in the source documents.

{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}

Michele Fedowitz, M.D.
Team Leader,
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CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D., Branch Chief
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CC:
Central Doc. Rm.
DO/Division Director/Wiley Chambers
DO/Deputy Director/William Boyd
DO/Medical Officer/Lucious Lim
DO/Medical Team Leader/Rhea Lloyd
DO/Project Manager/Michael Puglisi
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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COMPARATIVE ANALYSES, USE-RELATED RISK ANALYSIS, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA)

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:	March 23, 2023
Requesting Office or Division	Division of Ophthalmology (DO)
Application Type and Number:	NDA 217225
Product Name, Dosage Form and Strength:	Izervay[a] (avacincaptad pegol) injection, 20 mg/mL
Product Type:	Single Ingredient Combination Product (Drug-Device)
Device Constituent	Vial kit
Rx or OTC:	Rx
Applicant Name:	Iveric Bio, Inc. (Iveric)
FDA Received Date:	November 3, 2022
TTT #:	2022-2739 and 2022-2742
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Human Factors Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] The proprietary name for this NDA, Izervay was found conditionally acceptable on February 10, 2023. Izervay is used throughout this review.

1. REASON FOR REVIEW

This review evaluates the comparative analyses (CA), use-related risk analysis (URRA), labels and labeling, submitted under 505(b)(1) New Drug Application (NDA) 217225 for Izervay injection 20 mg/mL to determine whether Iveric needs to submit the results of a human factors (HF) validation study as a part of the marketing application. The Division of Ophthalmology (DO) requested that we review the URRA, CA, and labels and labeling for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT DESCRIPTION

Table 1 presents relevant product information for Izervay received on November 3, 2022, from Iveric.

Table 1. Relevant Product Information for Izervay

Product Name	**Izervay**
Application #	NDA 217225
Initial Approval Date	N/A
Active ingredient	Avacincaptad pegol
Indication	Treatment of Geographic Atrophy (GA) secondary to Age-Related Macular Degeneration (AMD).
Route of Administration	Intravitreal injection
Dosage Form	Injection
Strength	20 mg/mL
Dose and Frequency	2 mg (0.1 mL of 20 mg/mL solution) once monthly (approximately every 28 ± 7 days).
How Supplied	Each carton (NDC 82829-002-01) contains • One single-dose glass vial • One sterile 5-micron transfer filter needle (19-gauge x 1½ inch, 1.1 mm x 40 mm) • One sterile 1 mL Luer lock syringe. • One Prescribing Information (PI) Sterile, clear to slightly opalescent, colorless to slightly yellowish 20 mg/mL solution in a single-dose glass vial. Each glass vial contains

	an overfill amount to allow administration of a single 0.1 mL dose of solution containing 2 mg of Avacincaptad pegol (oligonucleotide basis).
Storage	Refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Do not shake. Keep the vial in the original carton to protect from light. Prior to use, the unopened glass vial may be kept at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours. Ensure that the injection is given immediately after preparation of the dose.
Intended Users	(b) (4)
Intended Use Environment	(b) (4)

2. MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review. The Appendices provide additional information.

Table 2. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA)	B
Use-related Risk Analysis and Comparative Analyses	C
Information Requests Issued During the Review	D – N/A
CDRH Human Factors Consult Review	E – N/A
Product Sample, Label and Labeling, Packaging	F

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the comparative analyses and URRA.

[redacted] (b) (4)

We find that the comparative analyses are not acceptable because [redacted] (b) (4) As such, for this particular proposed product, we determine that the URRA is adequate to inform our determination regarding HF data needs (see section 3.2 below).

[b] Draft Guidance for Industry: Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications. 2018. Available from: https://www.fda.gov/media/122971/download

3.2 USE-RELATED RISK ANALYSIS (URRA)

Iveric submitted a URRA which identified and evaluated the tasks involved in the use of their proposed product, the errors that users might commit, the tasks they might fail to perform and the potential negative consequences of use errors. Iveric assessed risk associated with the task in the URRA and determined that the risks are mitigated through labeling and device design.

We reviewed the URRA for the proposed product and based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what Iveric proposes for the design and intended use of this product. We note that the risk mitigations are similar labeling mitigation used for currently marketed vial kit intravitreal injection products and we are not aware of medication error concerns or other safety issues related to these products. Furthermore, we did not identify any additional use-related issues that were not analyzed in Iveric's URRA. Based on Iveric's identified use-related risks for this product, we determined the risks are mitigated by the proposed labels, labeling (b) (4) .

4. URRA CONCLUSION

Our review of the use-related risk analysis did not identify any new, differing, or unique risks for Izervay injection. As such, we agree with Iveric's justification for not submitting human factors validation study results to support their marketing application. We have no Human Factors recommendation for this NDA.

5. LABELS AND LABELING

The proposed trade and professional sample 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 5.1 for Iveric Bio, Inc.

5.1 RECOMMENDATIONS FOR IVERIC BIO. INC.

Table 3. Identified Issues and Recommendations for Iveric Bio. Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Professional Sample and Trade Container Label(s) and Carton Labeling			
1.	As currently presented, we note the use of the package type term [redacted] (b) (4)	[redacted] (b) (4) is not considered an appropriate package type term.[c]	Revise the package type term to "Single Dose."
Trade and Professional Sample Carton Labeling			
1.	As currently presented the strength statement of the professional sample and trade container labels reads "2 mg 0.1 mL of 20 mg/mL." 2 mg 0.1 mL of 20 mg/mL	Per USP General Chapter <7> Labeling, for container that hold a volume of less than 1 mL, the quantity per fraction of milliliter should be the only expression of strength.[d]	Revise the strength statement to remove 20 mg/mL such that the strength statement appears as "2 mg/0.1 mL" only.
2.	The usual dosage statement is not included.	21 CFR 201.55 requires that labels for prescription drug bear a statement of the recommended or usual dosage.	Add your intended "Recommended Dosage" statement. For example, "Recommended Dosage: See prescribing information."

[c] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient -Use Containers for Human Use. 2018 Available from: https://www.fda.gov/media/117883/download

[d] United States Pharmacopoeia (USP) General Chapter <7> Labeling

Table 3. Identified Issues and Recommendations for Iveric Bio. Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
3.	As currently presented, the storage requirement is not included.	Appropriate storage information can help mitigate the risk of wrong storage medication errors.	Include the storage information as described in the Prescribing Information. For example: Must be refrigerated at 2°C to 8°C (26°F to 46°F)
4.	As currently presented, the product identifier is missing.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[e] The DSCSA guidance on product identifiers recommends that the human-readable portion be located near the 2D data matrix barcode and recommends the following format: NDC: [insert product's NDC]

[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Iveric Bio. Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date] If you determine that the product identifier requirements apply to your product's labeling, we request you include product identifier along with the 2-D data matrix barcode. Additionally, ensure that there is sufficient white space between the linear barcode and 2-D data matrix barcode to allow barcode scanners the ability to correctly read each barcode.
5.	The lot number and expiration date are missing.	The lot number and expiration date are required per 21 CFR 203.38(a) and 21 CFR 211.137, respectively.	Include the lot number and expiration date. Additionally, ensure the lot number is clearly differentiated from the expiration date. See previous recommendation.

6. LABEL AND LABELING CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Section 5.1 for Iveric Bio., Inc. We ask that the Division of Ophthalmology convey Section 5.1 in its entirety to Iveric Bio., Inc. We advise these recommendations are implemented during this review cycle of NDA 217225. These revisions can be implemented without submission of HF data for Agency review.

APPENDICIES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. BACKGROUND INFORMATION/PREVIOUS HF REVIEWS (DMEPA)

A.1 PREVIOUS REVIEWS RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

A.1.1 Methods

On December 14, 2022, we searched the L: drive using the term NDA 217225 and Avacincaptad pegol to identify reviews previously performed by DMEPA.

A.1.2 Results

Our search did not identify any previous reviews.

A.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

Meeting	Summary of Relevant Recommendations
Type-B, Pre-NDA meeting date May 27, 2022[f]	Iveric stated that it is considering co-packaging components such as transfer filter needle, injection needle and empty syringe, with the drug product vial. Iveric asked the Agency to confirm that the proposed presentation would be regulated as combination product. Additionally, Iveric asked if the proposed documentation was adequate to support NDA. • Agency responded that the co-packaged product would be regulated as combination product. • Additionally, DMEPA commented that as product is proposed to be co-packaged and is considered combination product, we recommended that Iveric submit a URRA and a CA as justification for not conducting HF validation study.

We considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES

The URRA and comparative analyses can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda217225\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ga-amd\5354-other-stud-rep\hfe\hfe-report.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX E. CDRH HUMAN FACTORS CONSULT REVIEW

N/A

[f] Puglisi, M. Meeting Minutes – for IND 77902 (Avacincaptad pegol). Silver Spring (MD): FDA, CDER, OSE (US); 2022 JUN 16. IND 77902.

APPENDIX F. PRODUCT SAMPLE, LABELS AND LABELING, AND PACKAGING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Izervay labels and labeling submitted by Iveric on November 3, 2022, November 22, 2022, December 19,2022, and February 7, 2023:

- Container label
- Carton labeling
- Professional Sample Container label and Carton Labeling
- Prescribing Information (Image not shown), available from:
    - Annotated version: \\CDSESUB1\EVSPROD\nda217225\0005\m1\us\114-labeling\draft-labeling\annot-draft-label-text\annot-draft-label-text.pdf
    - Clean version: \\CDSESUB1\EVSPROD\nda217225\0004\m1\us\114-labeling\draft-labeling\draft-label-text\uspi-draft-label-text.pdf

F.2 Labels and Labeling Images

Trade container label

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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
03/24/2023 02:02:39 PM

VALERIE S VAUGHAN
03/24/2023 02:16:43 PM

OLUWAMUREWA OGUNTIMEIN
03/25/2023 04:13:05 PM

JASON A FLINT
03/25/2023 06:07:45 PM