CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 217225
Assessment # 1

Drug Product Name	Avacincaptad pegol Intravitreal Injection
Dosage Form	Injection
Strength	2 mg/0.1 ml (20 mg/ml)
Route of Administration	Intravitreal injection
Rx/OTC Dispensed	Rx
Applicant	IVERIC bio, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Nov 3, 2022	All disciplines
Quality Amendment	Jan 24, 2023	Quality microbiology
Quality Amendment	Feb 14, 2023	Drug substance, manufacturing process
Quality Amendment	Mar 7, 2023	Quality microbiology
Quality Amendment	Mar 10, 2023	Drug product
Quality Amendment	April 6, 2023	Manufacturing process
Quality Amendment	April 12, 2023	Drug product
Quality Amendment	May 12, 2023	Manufacturing process
Quality Amendment	May 15, 2023	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Joseph Leginus	Sithamalli Chandramouli
Drug Product	Dhanalakshmi Kasi	Chunchun Zhang
Manufacturing	Allison Aldridge	Sateesh Sathigari
Microbiology	Dacie Bridge	Yan Zheng
Biopharmaceutics	NA	
Regulatory Business Process Manager	Shazma Aftab	

Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Dhanalakshmi Kasi	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	NA		
	III			NA		
	III			NA		
	V			NA		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	77902	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics		NA		
Pharmacology/Toxicology		Acceptable	5/10/2023	Maria Rivera
CDRH		NA		
Clinical		NA		
Other		NA		

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects.

The product is regulated as a drug device combination product per the Genus decision. Needles and syringes are 510k-cleared or 510k exempt and CDRH confirmed a consult was not necessary on 1/25/2023. OPMA has issued an overall acceptable recommendation for all the facilities on 5/2/2023. Therefore, NDA 217225 is recommended approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Avacincaptad pegol Intravitreal Injection, 2 mg/0.1ml (20 mg/ml) is stored in a 2 ml type (b) (4) single dose glass vial with (b) (4) ml fill which is co-packaged with 1 mL, syringe and a Gauge, 1½ inch filter needle in a secondary carton.

Proposed Indication(s) including Intended Patient Population	For treatment of Geographic Atrophy (GA) secondary Age-related Macular Degeneration (AMD).
Duration of Treatment	Deliver 2 mg by intravitreal injection to each affected eye once monthly
Maximum Daily Dose	2mg; As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance Avacincaptad pegol is PEGylated 39-mer phosphodiester oligonucleotide. It is a white to almost white to pale yellow solid in (b) (4) All the CMC information including manufacturing process, specifications and stability data are found acceptable.

Drug Product: Adequate

Avacincaptad pegol intravitreal injection, 2 mg/0.1ml (20 mg/mL) is a sterile, colorless to slightly yellow solution. All the excipients are compendial.

The revised drug product specifications are acceptable and include the following quality attributes: appearance, clarity, color, identification, assay, visible particles, osmolality, pH, particulate matter, impurities/degradants, bacterial endotoxin, extractable volume, content uniformity, viscosity and sterility. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities and [redacted] (b) (4) impurities showed low risk. Extractable/leachable studies were performed; none of the extracted substances have a level of concentration above the safety level.

Avacincaptad pegol intravitreal injection, 2 mg/0.1ml is packaged in 2 mL single dose glass vials, with a rubber stopper and aluminum overseal, which is then co-packaged with two device constituent parts (a sterile 1 mL, [redacted] (b) (4) Luer-LokTM empty syringe and a sterile, [redacted] (b) (4) 19 Gauge, 1½ inch filter needle) to form the final product kit. Reference to the 510k clearance for the devices including syringe and needle are provided. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted one drug product primary stability batch with 24 months stability data and two batches with 12 months data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°C/60%RH). All the quality attributes met the specifications. Photostability study indicated that the product is photo-sensitive and freeze-thaw study with three cycles were conducted to indicate the product is stable, however it should be stored at the refrigerated condition. Therefore, the expiration date of 24 months for commercial products is granted when stored at 2 °C to 8 °C (36 °F to 46 °F) with cautionary statements “Do not freeze. Do not shake. Keep the vial in the original carton to protect from light”.

The storage statement is “Store at 2 °C to 8 °C (36 °F to 46 °F).” and will be finalized at the OND’s labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The manufacturing process includes (b) (4) All the process related concerns have been resolved. All the manufacturing sites are acceptable based on the inspection history and manufacturing capability. OPMA has issued an overall acceptable recommendation for all the facilities on 5/2/2023.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The drug product is (b) (4) Sterility and bacterial endotoxins are tested for release of finished drug product.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials	L	(b) (4)	L	
Impurities	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	
Particulate matter	• Formulation • Container closure	L		L	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	
Bacterial Endotoxin	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., May 19, 2023

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Established name(s) Route(s) of administration	TRADENAME® (avacincaptad pegol) injection, for intravitreal use	IZERVAY (avacincaptad pegol) injection, for intravitreal use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 20 mg/mL solution in a single-dose vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

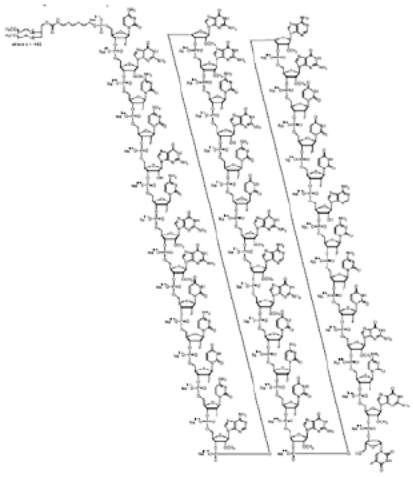
1.2 FULL PRESCRIBING INFORMATION

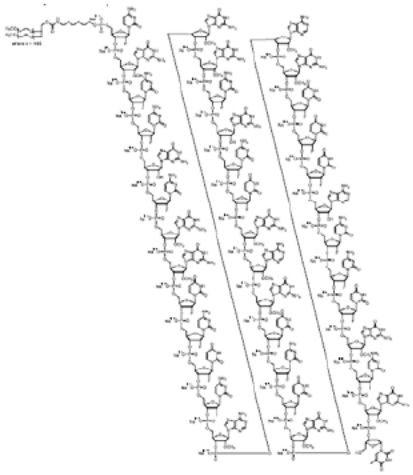
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.	Injection: 20 mg/mL clear, colorless to slightly yellow solution in a single-dose vial.
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	IZERVAY contains avacincaptad pegol sodium, a complement C5 inhibitor. Avacincaptad pegol is a ribonucleic acid (RNA) aptamer, covalently bound to a (b) (4) kiloDalton (kDa) branched polyethylene glycol (PEG) molecule.	IZERVAY contains avacincaptad pegol sodium, a ribonucleic acid (RNA) aptamer, covalently bound to a (b) (4) -kiloDalton (kDa) branched polyethylene glycol (PEG) molecule is a complement C5 inhibitor. Avacincaptad pegol sodium has a molecular formula of $C_{395}H_{492}N_{142}O_{262}P_{39}F_{21}((CH_2)_2O)n$, (n~970), a molecular weight is approximately 56 kDa and the following structural formula:
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The molecular formula of avacincaptad pegol (free acid form) is C395H492N142O262P39F21((CH2)2O)n where n~970 and the molecular weight is approximately 56 kDa. The structure of avacincaptad pegol sodium is presented below.	.  IZERVAY is a sterile, clear colorless to slightly yellowish solution in a single-dose glass vial for intravitreal administration available as 20
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		



Other important chemical or physical properties (such as pKa or pH)	IZERVAY (avacincaptad pegol injection) is a sterile, clear to slightly opalescent, colorless to slightly yellowish solution in a single-dose glass vial for intravitreal administration. Each single-dose vial is designed to deliver 0.1 mL of solution containing 2 mg avacincaptad pegol (oligonucleotide basis), 0.198 mg dibasic sodium phosphate heptahydrate, 0.0256 mg monobasic sodium phosphate monohydrate, and 0.83 mg sodium chloride. IZERVAY is formulated in Water for Injection, with a target pH of 7.3. IZERVAY does not contain an anti-microbial preservative.	mg/mL. Each mL contains 2 mg avacincaptad pegol (oligonucleotide basis),0.198 mg dibasic sodium phosphate heptahydrate, 0.0256 mg monobasic sodium phosphate monohydrate, and 0.83 mg sodium chloride and Water for Injection, with a target pH of 7.3

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	IZERVAY (avacincaptad pegol) injection is supplied as a 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). Each IZERVAY carton (NDC 82829-002-01) contains one glass vial, one sterile 5-micron transfer filter needle (19-gauge x 1½ inch, 1.1 mm x 40 mm), and one sterile 1 mL Luer lock syringe. Store IZERVAY in the 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 of IZERVAY 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.	IZERVAY is available as 20 mg/mL solution in a single-dose glass vial. NDC 82829-002-01: One glass vial, one sterile 5-micron transfer filter needle (19-gauge x 1½ inch, 1.1 mm x 40 mm), and one sterile 1 mL Luer lock syringe. Store IZERVAY in the 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 of IZERVAY may be kept at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours. Discard unused portions.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	IZERVAY™ (avacincaptad pegol) Manufactured by: IVERIC bio, Inc. 8 Sylvan Way Parsippany, NJ 07054	Manufactured by: IVERIC bio, Inc. 8 Sylvan Way Parsippany, NJ 07054

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

No Information included.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)

Assessment of Carton and Container Labeling: *Adequate*

The following recommendations are made:
1.Carton and vial label says, [redacted] (b) (4) while the PI says "single dose vial". [redacted] (b) (4) is not the correct term. Hence, carton and container label needs to be revised to match with the PI.
2. "2 mg/0.1 mL of 20 mg/mL needs to be revised to 2 mg/0.1 mL.
3. Lot number and expiry date needs to be included.

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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Chunchun Zhang

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	217225
Assessment Cycle Number	01
Drug Product Name/ Strength	IZERVAY (Avacincaptad pegol) injection, 20 mg/mL
Route of Administration	Intravitreal Injection
Applicant Name	IVERIC bio, Inc
Therapeutic Classification/ OND Division	
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
1	11/3/2022 (ORIG-1)
5	12/19/2022 (CMC Submission)
6	1/24/2023 (Quality Response to Micro IR Request)
8	2/7/2023 (Labeling)
10	3/7/2023 (Quality Response to Micro IR Request)

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable

Remarks: This is a 505(b)(1) submission. Links were provided to previous meeting correspondences, including CMC only meetings, in Sequence 0001. The submission is rolling submission with a Priority Review.

The proposed drug product is a drug-device combination product used for intravitreal injection. Type C meeting responses dated 7/14/2022 states that to rely on sterilization and package integrity of the device manufacturer, reference to the 510k clearance for the device should be provided, any processing or assembly steps undertaken with devices and rationale for how these are unlikely to impact packaging integrity of the sterile devices should be provided, and it was noted that the endotoxin specifications may not be adequate with reference to the Agency's Guidance "*Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices*."

As this is a rolling submission, the CMC information was provided in Sequence 005, Supporting Document 5.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): Not applicable

Supporting Documents:

- [redacted]
- [redacted] adequate) for buildings and facilities, [redacted]

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**
  (P.1: Description and Composition of the Drug Product)

  Avacincaptad pegol, 20 mg/mL is a preservative-free, sterile, aqueous solution intended for single-dose intravitreal administration. The solution is packaged in 2 mL glass vials, with a rubber stopper and aluminum overseal, which is then co-packaged with two device constituent parts (a sterile 1 mL, [redacted] Luer-Lok™ empty syringe and a sterile, [redacted] 19 Gauge, 1½ inch filter needle) to form the final product kit.

- **Drug Product Composition**
  (P.1: P.1: Description and Composition of the Drug Product; P.3.2: Batch Formula)

Ingredient	Function	Quantity/vial	Quantity/mL
Avacincaptad Pegol (Oligonucleotide basis; In house)	API	[redacted]	20 mg
Dibasic Sodium Phosphate Heptahydrate (USP)	[redacted]		1.98 mg
Monobasic Sodium Phosphate Monohydrate (USP)			0.256 mg
Sodium Chloride (USP, Ph. Eur.)			8.3 mg
Water for Injection (USP, Ph. Eur.)			q.s.

- **Description of Container Closure System**
  (P.7: Container Closure System-Vial, Container Closure System-Kit)

Component	Description	Manufacturer
Vial	2 mL [redacted] clear, USP Type [redacted] glass vial	[redacted]
Stopper	13 mm [redacted] rubber stopper, [redacted]	
Seal	13 mm aluminum seal with flip-off cap	
Syringe	Sterile, 1 mL [redacted] Luer-LokTM empty syringe [redacted]	
Filter Needle	Sterile, [redacted] 19 Gauge, 1½ inch filter needle [redacted]	

Assessment: ***Adequate***

P.2 PHARMACEUTICAL DEVELOPMENT

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Assessment: *Adequate*

- **Comparability Protocols-** Not applicable

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

(Seq. 0008: 1.14.1.1: Carton Commercial, Carton Sample, Vial Commercial, Vial Sample; Seq. 0005: Annotated Draft Labeling Text)

- **Dosage and Administration**:

- **Carton/Container Labeling-**
  - **Strength:**
    - Carton: (b) (4)

    - Vial: 2 mg, 0.1 mL of 20 mg/mL
  - **Dosage:** [redacted] (b) (4)
  - **Route of administration:** For Intravitreal Injection.
  - **Storage temperature:** [redacted] (b) (4) refrigerator 2-8 °C (26-46°F) in the original carton to protect from light. Do not freeze. Do not shake. Prior to use the unopened glass vial of IZERVAY may be kept at room temperature (20-25°C / 68-77 °F) for up to 24 hours.
  - **Other:** [redacted] (b) (4) Discard unused portion.
  - **Carton:** Carton contains: One IZERVAY vial, one filter needle, and one syringe.

Assessment: *Adequate*

- **Post-Approval Commitments-** Not applicable

MICROBIOLOGY LIST OF DEFICIENCIES

Not Applicable

Primary Microbiology Assessor Name and Date*:* Dacie R. Bridge, Ph.D. March 10, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed)*:* Yan Zheng, Ph.D., March 10, 2023

Dacie Bridge

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Yan Zheng

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