CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 217202 Resubmission (Sequence 33)

Executive Summary

1. Application/Product Information

NDA Number.	217202		
Applicant Name	AOP Orphan Pharmaceuticals GmbH		
Drug Product Name	Landiolol		
Dosage Form.	Injection		
Proposed Strength(s)	280 mg per vial		
Route of Administration	Intravenous		
Maximum Daily Dose	2,688 mg/day (as free base)		
Rx/OTC Dispensed	Rx		
Proposed Indication	A beta adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.		
Drug Product Description	Sterile lyophilized powder in a single dose glass vial.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68ºF to 77ºF)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen	Zhengfu Wang
	Drug Product/ Labeling	Dan Berger	Theodore Carver
	Manufacturing	Allison Aldridge	Rose Xu

	Biopharmaceutics	N/A; see previous IQA	N/A; see previous IQA
	Microbiology	N/A; see previous IQA	N/A; see previous IQA
	Other (specify):	N/A	
	RBPM	Grafton Adams CDER/OPQ/OPRO/DRBPMI	
	ATL	Theodore Carver CDER/OPQ/OPQAI/DPQAII	
Consults	N/A		

2. . Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the Landiolol drug product when stored at 25^{o}C.

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

AOP Orphan Pharmaceuticals submitted NDA 217202 on May 29, 2022, seeking marketing approval for landiolol HCl lyophilized powder for injection, which is a beta-1 adrenergic receptor blocker indicated for short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. This NDA was submitted as 505(b)(2) application, and Landiolol is a new molecular entity in the U.S. On May 31, 2023, FDA issued a Complete Response for NDA 217202 due to drug product and manufacturing deficiencies. The NDA was resubmitted on May 29, 2024, including responses to the deficiencies identified in the original

review. The review team for the NDA resubmission included drug substance, drug product, and manufacturing reviewers.

1.) Drug Substance (landiolol hydrochloride)

Landiolol hydrochloride is a small synthetic molecule that is structurally well-characterized with two stereocenters. Polymorphic form and particle size are not attributes that affect the drug product (b) (4) (b) (4). Due to the presence of a (b) (4) in the landiolol drug product, (b) (4), the review team determined that control of this impurity in the drug substance specification is needed. The applicant has included a limit of NMT (b) (4) ppb for (b) (4) in the drug substance specification, which was determined to be adequate to support the limit in the drug product. The drug substance manufacturing process, materials and reagents, controls, and specification remain adequate. The updated drug substance stability data support a retest date of (b) (4) months for the drug substance when stored at (b) (4).

2.) Drug Product (Landiolol injection)

The drug product for injection is a sterile, white to almost white lyophilized powder containing 280 mg of landiolol (provided as 300 mg of landiolol hydrochloride) and 300 mg mannitol. After reconstitution, the drug product is administered intravenously using a syringe pump. The original drug product review identified a potential (b) (4) impurity (b) (4) (b) (4), and the maximum daily exposure to this impurity resulting from the levels reported by the Applicant for primary drug product lots exceeded the acceptable daily intake for this impurity recommended by the nonclinical review team. Based upon an agreed upon higher AI limit of (b) (4) ng/day in discussions between the Agency and the Applicant (see minutes from Type A meeting held on October 27, 2023), the Applicant's proposed acceptance criterion of (b) (4) ppb was determined to be acceptable. In addition, the Applicant proposed revised acceptance criteria for (b) (4) in the drug product specification, and the drug product review determined the final specification to be acceptable to ensure product quality. Therefore, all deficiencies in the NDA have been addressed from the drug product perspective. Additional stability data in the NDA resubmission confirmed that the proposed shelf-life of 24 months at 25°C is acceptable, including the levels of (b) (4) through the shelf life. The NDA is adequate from the drug product perspective.

3.) Manufacturing

Process – The drug product manufacturing process includes [redacted] (b) (4) [redacted] (b) (4). The review of the resubmission concluded that process deficiencies related to the [redacted] (b) (4) [redacted] (b) (4) limits, in-process controls, and [redacted] (b) (4) limits have been resolved and the process is adequate to support the drug product quality.

Facilities – All facilities were found to be acceptable based on previous history, except for the drug product manufacturing facility Lyocontract GmbH (FEI: 3014034890). The drug product manufacturing facility was inspected from May 15 to 25, 2023, with a final approval recommendation. Therefore, the overall recommendation is approval for all manufacturing facilities.

4.) Biopharmaceutics

The biopharmaceutics review previously concluded that the comparative physicochemical data in the NDA support a scientific bridge between the proposed landiolol 280 mg product and Onoact® 50 for injection. Since there are no changes that would affect the scientific bridge in the NDA resubmission, no biopharmaceutics revie of the NDA resubmission was required, and it remains adequate from the biopharmaceutics perspective.

5.) Microbiology

There were no changes to the NDA that would affect the microbiological controls, and therefore no additional microbiological review was required. The NDA remains adequate from the microbiology perspective.

6.) Quality Labeling

The review of the quality aspects of the drug product labeling concluded that the labeling will be adequate after agreed upon changes have been implemented, and there are no outstanding labeling deficiencies from the CMC perspective.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**

Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None.

Theodore Carver

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Following edits made to the highlights, sections 2, 3, 11 and 16, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	BRANDNAME	Adequate
Established name(s)	Landiolol	Adequate
Route(s) of administration	For injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	280 mg as a lyophilized powder in a single-dose vial	Adequate following edits to correct spelling of "lyophilized"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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.	NA	NA

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)	Reconstitute each 280 mg vial of BRANDNAME with 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently swirl to dissolve contents. Use immediately. Discard unused portion.	Adequate, following edits made. Additionally recommended to change dosing in Table 1 from 9.3 mcg/kg/min to 9 mcg/kg/min

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)	For injection	Adequate
Strength(s) in metric system	280 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Salt policy applied	Adequate, following edits made
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to almost white lyophilized powder in a single-dose vial containing 280 mg of landiolol (equivalent to 300 mg landiolol HCl).	Adequate, following edits made
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BRANDNAME, landiolol	Adequate following edits made
Dosage form(s) and route(s) of administration	Lyophilized powder for intravenous injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	280 mg landiolol HCl (equivalent to 300 mg landiolol HCl)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Mannitol and sodium hydroxide	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	300 mg mannitol and sodium hydroxide as needed to adjust pH	Adequate following edits made
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	Sterile lyophilized powder	Adequate following edits made
Pharmacological/ Therapeutic class	Beta-1 adrenergic receptor blocker	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{25}H_{39}N_3O_8 \cdot HCl$, 546.06.	Adequate with recommendation to add clean structure
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Very soluble in water.	Adequate

* •[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 3-[4-[(2S)-2-hydroxy-3-[2-(morpholine-4-carbonylamino)ethylamino]-propoxy]phenyl]propionate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 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)	Lyophilized powder for injection.	Adequate with edits made
Strength(s) in metric system	280 mg per vial	Adequate
Available units (e.g., bottles of 100 tablets)	Single-dose vial containing 280 mg landiolol	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to almost white lyophilized powder, NDC xxxxx-xx-xx	Adequate following DMEPA recommendation to add "preservative-free"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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.	Single-dose vial	Adequate

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.)	NA	NA
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."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	Adequate
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."	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 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	Manufactured for: AOP Orphan Pharmaceuticals GmbH, Leopold-Ungar-Platz 2, 1190 Vienna, Austria	Adequate.

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about vial and carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Tradename (landiolol)	Adequate
Dosage strength	280 mg/vial	Adequate, following DMEPA edits
Route of administration	For injection	Adequate, with recommendation to place after "(landiolol)"
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each vial contains 280 mg landiolol (equivalent to 300 mg landiolol hydrochloride)	Adequate following recommended edits
Net contents (e.g. tablet count)	280 mg of landiolol	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Not present	Adequate, following DMEPA comment

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Manufactured by: Lyocontract GmbH, Pulverwiese 1, 38871 Ilsenburg, Germany	Adequate
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*
DMEPA and CMC recommendations have been made to address carton and vial labeling. With the required edits, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All edits to the carton and container labels have been completed or are currently addressed by DMEPA and CMC comments. The Prescribing Information, Medication Guide and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger, Ph.D. September 27, 2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Theodore Carver, Ph.D. September 27, 2024

Dan Berger

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NDA Executive Summary (Review #2 of Original NDA)

1. Application/Product Information

NDA Number.	217202		
Applicant Name	AOP Orphan Pharmaceuticals GmbH		
Drug Product Name	Landiolol		
Dosage Form.	Injection		
Proposed Strength(s)	280 mg		
Route of Administration	Intravenous		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	A beta adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.		
Drug Product Description	Sterile lyophilized powder in a single dose glass vial.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68ºF to 77ºF)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen OPQ/ONDP/DNDAPI/NDB3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Dan Berger OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	Manufacturing	Allison Aldridge OPQ/OPMA/DPMAIV/PMB12	Rose Xu OPQ/OPMA/DPMAIV/PMB12
	Biopharmaceutics	Zhuojun (Joan) Zhao OPQ/ONDP/DB/BB3	Haritha Mandula OPQ/ONDP/DB/BB3

	Microbiology	Aditi Das OPQ/OPMA/DMAI/MAB2	Yuansha Chen OPQ/OPMA/DMAI/MAB2
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

This Integrated Quality Assessment (IQA) #2 includes the final manufacturing review and serves as an addendum to the Integrated Quality Review #1 filed on April 21, 2023. The final overall recommendation is a Complete Response due to the product quality and manufacturing deficiencies listed below. This list is complete with respect to all deficiencies identified during the quality review of this NDA.

3. Deficiencies

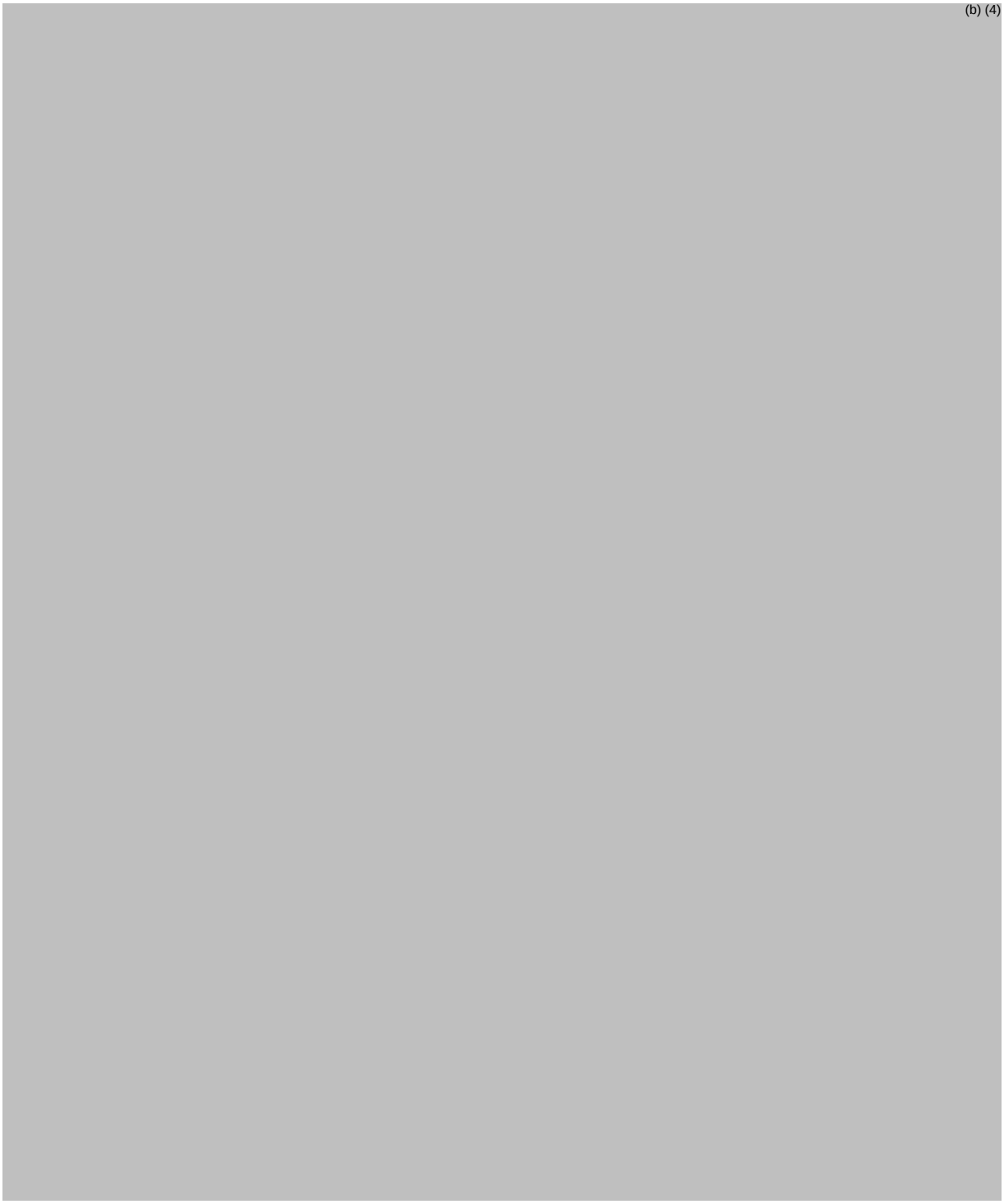
Product Quality

(b) (4)

[redacted]

Manufacturing

(b) (4)



4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

AOP Orphan Pharmaceuticals has submitted NDA 217202 seeking marketing approval for landiolol HCl lyophilized powder for injection, which is a beta-1 adrenergic receptor blocker indicated for short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. This IQA #2 of this NDA communicates the conclusion of the manufacturing review. All other reviews and review summaries may be found in IQA #1 filed on April 21, 2023.

2.) Manufacturing.

Process – The drug product manufacturing process includes (b) (4) (b) (4). The proposed commercial batch scale is (b) (4). During the review, the review team was unable to satisfactorily resolve deficiencies in the Applicant's approach (b) (4) (b) (4) after several cycles of information requests and responses. In addition, there were deficiencies in the in-process controls and (b) (4) limits reported in the Master Batch Record. The review team recommended that the manufacturing not be approved until these deficiencies are resolved (see list of deficiencies above).

Facilities – All facilities were found to be approvable based on previous history except for the drug product manufacturing facility Lyocontract GmbH (FEI: 3014034890), which was inspected from May 15th to 25th, 2023 (preapproval inspection for this NDA). There were several deficiencies noted related to equipment qualification, testing, and record keeping, with a final approval recommendation based on communications with the facility during the inspection regarding corrective actions to be taken. The final overall facilities recommendation is approval.

3.) Quality Labeling

The review of the quality aspects of the drug product labeling concluded that the labeling will be adequate after the manufacturer agreed to implement recommended changes. The labeling will not be finalized until all deficiencies have been addressed in a subsequent review.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Inadequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Inadequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: Not applicable.

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NDA Executive Summary

1. Application/Product Information

NDA Number.	217202		
Applicant Name	AOP Orphan Pharmaceuticals GmbH		
Drug Product Name	Landiolol		
Dosage Form.	Injection		
Proposed Strength(s)	280 mg		
Route of Administration	Intravenous		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	A beta adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.		
Drug Product Description	Sterile lyophilized powder in a single dose glass vial.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68ºF to 77ºF)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen OPQ/ONDP/DNDAPI/NDB3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Dan Berger OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	Manufacturing	Allison Aldridge OPQ/OPMA/DPMAIV/PMB12	Rose Xu OPQ/OPMA/DPMAIV/PMB12
	Biopharmaceutics	Zhuojun (Joan) Zhao OPQ/ONDP/DB/BB3	Haritha Mandula OPQ/ONDP/DB/BB3

	Microbiology	Aditi Das OPQ/OPMA/DMAI/MAB2	Yuansha Chen OPQ/OPMA/DMAI/MAB2
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

This Integrated Quality Assessment (IQA) #1 includes a pending review of the manufacturing facilities, because a preapproval inspection of the drug product manufacturing facility has not yet been completed; however, the final overall recommendation is a Complete Response due to the product quality and manufacturing deficiencies listed below that were identified in this IQA.

2. Deficiencies

Product Quality

(b) (4)

(b) (4)

Manufacturing

(b) (4)

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

AOP Orphan Pharmaceuticals has submitted NDA 217202 seeking marketing approval for landiolol HCl lyophilized powder for injection, which is a beta-1 adrenergic receptor blocker indicated for short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. This NDA is submitted as 505(b)(2) application because it relies upon published information and marketing approval in the EU to support approval in the U.S. Although approved in other regions, Landiolol HCl is a new molecular entity in the U.S.

1.) Drug Substance (landiolol hydrochloride)

Landiolol hydrochloride is a small synthetic molecule that is structurally well-characterized with two stereocenters It is manufactured as the (b) (4) stereoisomer and in a single polymorphic form. Polymorphic form and particle size are not attributes that affect the drug product (b) (4) (b) (4) The drug substance manufacturing process, materials and reagents, controls, and specification were found to be adequate. All impurities are either qualified or controlled per ICH Q3 guidances or ICH M7 for genotoxic impurities. The stability data support a retest date of (b) (4) months for the drug substance.

2.) Drug Product (Landiolol injection)

The drug product for injection is a sterile, white to almost white lyophilized powder containing 280 mg of landiolol (provided as 300 mg of landiolol hydrochloride) and 300 mg mannitol. The lyophilized drug product is filled in Type (b) (4) 50 mL glass vials sealed with (b) (4) rubber stoppers and aluminum flip-off caps, and the powder is reconstituted with 50 mL of 0.9% saline prior to use. The product is administered intravenously using a syringe pump. The drug product review identified a potential (b) (4) impurity (b) (4) (b) (4) (b) (4), which the Applicant addressed by providing test data indicating levels of (b) (4) to (b) (4) ppb in drug product lots. The maximum daily exposure to this impurity resulting from these levels exceeds the acceptable intake of (b) (4) ng/day, based on a (b) (4) g daily dose of landiolol. In addition, the proposed (b) (4) acceptance criteria proposed for the drug product specification remain deficient after the Applicant's responses to several rounds of information requests to address this issue (see list of deficiencies

above). Final assessment of stability data and assignment of shelf life will be performed when these deficiencies have been addressed, because the shelf life will depend on (b) (4) during storage.

3.) Manufacturing

Process – The drug product manufacturing process includes (b) (4) (b) (4). The proposed commercial batch scale is (b) (4). During the course of the review, the review team was unable to satisfactorily resolve deficiencies in the Applicant's approach to (b) (4), after several cycles of information requests and responses. In addition, there were deficiencies in the in-process controls and (b) (4) limits reported in the Master Batch Record. The review team recommended that the manufacturing no be approved until these deficiencies are resolved (see list of deficiencies above).

Facilities – All facilities were found to be approvable based on previous history except for the drug product manufacturing facility Lyocontract GmbH (FEI: 3014034890). This drug product facility has not undergone cGMP inspection for a drug product and therefore, this facility has been scheduled for a preapproval inspection scheduled for May 2023. Because this inspection is yet to be performed, the review conclusion for facilities is pending and therefore, the final manufacturing review conclusion is pending. However, the review conclusion of inadequate will not be affected by the facility inspection; and this review will be amended as needed if additional deficiencies are identified during the facility inspection.

4.) Biopharmaceutics

Although the proposed 280 mg landiolol for injection has the same active ingredient, dosage form (b) (4) as the reference drug product. Onoact® 50 for injection, it differs in dose and dosing regimen, and a biowaiver under 21 CFR 320.22(b)(1) is not feasible. Therefore, the biopharmaceutics review focused on evaluation of the physicochemical data to support a scientific bridge between the proposed and reference drug products. The review concluded that the comparative physicochemical data in the NDA support a scientific bridge between the proposed landiolol 280 mg product and Onoact® 50 for injection.

5.) Microbiology

The microbiology review covered the (b) (4), microbiological quality and sterility assurance aspects of the landiolol drug product. The drug product is (b) (4). In response

to information requests, the Applicant provided data to support the container-closure integrity test, hold times, process and equipment validation, [redacted] (b) (4), and other aspects of the manufacturing process and added a [redacted] (b) (4). The microbiology review recommended approval of the NDA.

6.) Quality Labeling

The review of the quality aspects of the drug product labeling concluded that the labeling will be adequate after the manufacturer agreed to implement recommended changes. The labeling will not be finalized until all deficiencies have been addressed in a subsequent review.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Inadequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Pending**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: Not applicable currently.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Following edits made to the highlights, sections 2, 3, 11 and 16, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	BRANDNAME	Adequate
Established name(s)	Landiolol	Adequate
Route(s) of administration	For injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	280 mg per single-dose vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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.	NA	NA

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)	Reconstitute each 280 mg vial of BRANDNAME with 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently swirl to dissolve contents. Use immediately. Discard unused portion.	Adequate, following edits made

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)	For injection	Adequate
Strength(s) in metric system	280 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Salt policy applied	Adequate, following edits made
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to almost white lyophilized powder in a single-dose vial containing 280 mg of landiolol (equivalent to 300 mg landiolol HCl).	Adequate, following edits made
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BRANDNAME, landiolol	Adequate following edits made
Dosage form(s) and route(s) of administration	Lyophilized powder for intravenous injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	280 mg landiolol HCl (equivalent to 300 mg landiolol HCl)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Mannitol and sodium hydroxide to adjust pH	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	Mannitol (b) (4) (b) (4) (300 mg)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Beta-1 adrenergic receptor blocker	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{25}H_{39}N_3O_8 \cdot HCl$, 546.06.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Very soluble in water.	Adequate

* •[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 3-[4-[(2S)-2-hydroxy-3-[2-(morpholine-4-carbonylamino)ethylamino]-propoxy]phenyl]propionate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA

Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 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)	Lyophilized powder for injection.	Adequate with edits made
Strength(s) in metric system	280 mg per vial	Adequate
Available units (e.g., bottles of 100 tablets)	Single-dose vial containing 280 mg landiolol	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to almost white lyophilized powder, NDC xxxxx-xx-xx	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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.	Single-dose vial	Adequate

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.)	NA	NA
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.”	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	Adequate
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.”	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 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	Manufactured for: AOP Orphan Pharmaceuticals GmbH, Leopold-Ungar-Platz 2, 1190 Vienna, Austria	Adequate.

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about vial and carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4) (landiolol)	Adequate
Dosage strength	(b) (4)	Adequate, following DMEPA edits
Route of administration	For injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each vial contains 280 mg landiolol (equivalent to 300 mg landiolol hydrochloride)	Adequate following recommended edits
Net contents (e.g. tablet count)	280 mg of landiolol	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Not present	Adequate, following DMEPA comment

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Manufactured by: Lyocontract GmbH, Pulverwiese 1, 38871 Ilsenburg, Germany	Adequate
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*
DMEPA has agreed to address the required edits to the storage information. With the required edits, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All edits to the carton and container labels have been completed or are currently addressed by DMEPA comments. The Prescribing Information, Medication Guide and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger April 4, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Theodore Carver April 4, 2023

Dan Berger

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Theodore Carver

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	217202
Assessment Cycle Number	001
Drug Product Name/ Strength	Landiolol HCl, Lyophilized powder for injection (300 mg in 50 mL single-dose vial)
Route of Administration	Intravenous
Applicant Name	AOP Orphan Pharmaceuticals GmbH
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology (DCN)
Proposed Indication	For the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.

Assessment Recommendation: **Adequate**

Assessment Summary:

AOP Orphan Pharmaceuticals GmbH (AOP)'s NDA 217202 was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act. The Applicant relies on the efficacy assessment from the published literature, specifically for Onoact® 50 for injection, approved in Japan.

AOP's proposed Landiolol HCl, 300 mg for injection is a lyophilized powder, which has the same API, dosage form, and route of administration as Onoact® 50 for injection, but is different in dose and dosing regimen. Due to the difference, a biowaiver under *21 CFR 320.22(b)(1)* is not feasible. However, a bridge between the proposed drug product and Onoact® 50 for injection can be established based on *21 CFR 320.24 (b)(6)*.

The Biopharmaceutics review is focused on the evaluation of the overall data to support a scientific bridge between the proposed Landiolol HCl, Lyophilized powder for injection and Onoact® 50 for injection.

AOP's proposed Landiolol HCl, 300 mg for injection has the same excipient, mannitol, and relative ratio of Landiolol to mannitol (1:1) as Onoact® 50 for injection. The Applicant provided comparative physicochemical data, which showed comparable pH and osmolality between the proposed Landiolol HCl, 300 mg for injection and Onoact® 50 for injection.

Therefore, the Applicant has provided sufficient information to support the bridge between the proposed Landiolol HCl, 300 mg for injection and Onoact® 50 for injection under *21CFR 320.24 (b) (6)*.

List Submissions Being Assessed:

Document Assessed	Date Received
Original Submission (0001)	**September 1, 2022**

IR Response (0005)	**August 10, 2022**
IR Response (0009)	**October 28, 2022**
IR Response (0013)	**November 22, 2022**

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Solubility:

The Applicant investigated the solubility of drug substance, Landiolol Hydrochloride, in various solvents (Table 1).

Table 1: Solubility of Landiolol HCl

Solvent	Solubility (descriptive term) (*)	Volume of solvent for dissolving 1 g of solute (*)	Solubility range (mg/ml)
Water	Very soluble	Less than 1 mL	> 1000
Methanol	Very soluble	Less than 1 mL	> 1000
N,N-DMF	Freely soluble	From 1 to less than 10 mL	From 100 to 1000 (about 850)
Ethanol	Soluble	From 10 to less than 30 mL	From 33 to 100 (about 60)
Acetonitrile	Slightly soluble	From 100 to less than 1000 mL	From 1 to 10 (about 6)

Assessment: ***{Adequate}***

The drug substance, Landiolol Hydrochloride, is highly soluble in water.

B.2 FORMULATION

The proposed Landiolol HCl 300 mg for injection is a white to almost white lyophilized powder, containing 300 mg Landiolol, and an equal amount of Mannitol as shown in Table 2.

Table 2: Quantitative composition of Landiolol HCl 300 mg for injection

Name of ingredient	Quantity (per vial)	Function	Reference to Standards	% (w/v) Reconstituted solution	Concentration per mL Reconstituted solution
Landiolol hydrochloride (Landiolol)	300 mg (280 mg)	Active Pharmaceutical Ingredient	In-house specification	0.6	6 mg/mL
Mannitol (b) (4)	300 mg	(b) (4)	USP	0.6	6 mg/mL
Sodium hydroxide*	(b) (4)	pH adjustment	NF	(b) (4)	
Water for injection**	(b) (4)	(b) (4)	USP		

* (b) (4)

** Removed during lyophilization process

B.3 BRIDGING OF FORMULATIONS

The Applicant relies on the efficacy assessment from the published literature, specifically for Onoact® 50 for injection (approved in Japan).

The following information is evaluated in support of the bridging between the proposed Landiolol HCl 300 mg for injection and Onoact® 50 for injection:

1. Formulation, dosage form, and administered volume
2. Comparative physicochemical data

1) Formulation, dosage form and administered volume

The Applicant provided the comparative quantitative composition between the proposed Landiolol HCl 300 mg for injection (LDLL300) and Onoact® 50 for injection in IR response dated November 22, 2022[1].

Table 3: Comparative Compositions of Onoact® 50 before Dilution and AOP's Landiolol HCl 300 mg for injection

Formulation	Quantitative Composition / Dosage Unit prior Reconstitution / Dilution		Final Landiolol HCl Concentration and Volume after Reconstitution / Dilution	Administered volume / h (assuming 50 kg body weight)
	Active Ingredients	Inactive Ingredients		
LDLL300 lyophilizate (vial)	300 mg landiolol HCl	• Mannitol 300 mg • Sodium hydroxide	6 mg/mL, 50 mL	0.5 – 20 mL / h (1 – 40 mcg/kg/min)
Onoact 50 Lyophilizate (vial)	50 mg landiolol HCl	• Mannitol 50 mg • pH regulator (traces of Sodium)	10 mg/mL, 5 mL 2.5 mg/mL, 20 mL 1 mg/ mL, 50 mL	3 – 12 mL / h* (10 – 40 mcg/kg/min) 12 – 48 mL / h* (10 – 40 mcg/kg/min) 3 – 60 mL / h* (1 – 20 mcg/kg/min)

Assessment: {Adequate}

AOP's Landiolol HCl 300 mg for injection is proposed to be reconstituted with either 0.9% NaCl or 5% glucose solution, prior to use, while Onoact® 50 is reconstituted in 15 mL or more of physiological saline[2]. Based on the flexibility in preparation of the final concentration and administered volume of Onoact® 50 intravenous infusion, the proposed final concentration after reconstitution of 6 mg/mL of AOP's proposed Landiolol HCl 300 mg is within Onoact® 50's final concentration range of 1-10 mg/mL and thus deemed acceptable from Biopharmaceutics perspective.

The Applicant conducted clinical pharmacology studies as well as references published data in Onoact® clinical pharmacology studies to support the range of doses and dosing regimens, which will be assessed by the Office of Clinical Pharmacology.

2) Comparative Physicochemical Data

In the original submission, the Applicant used water for injection (WFI) as diluent for product release and stability studies. In response to CMC comments dated July 27, 2022, the Applicant provided data (Table 4) of Landiolol HCl 300 mg for injection (Registration batches L32103 and L32104) reconstituted with saline and glucose in submission dated August 10, 2022.

[1] \\CDSESUB1\EVSPROD\nda217202\0013\m1\us\111-information-amendment\response-to-fda-quality-information-request.pdf

[2] \\CDSESUB1\EVSPROD\nda217202\0000\m5\54-lit-ref\onoact-pharmaceutical-interview-form-2020.pdf

Table 4: Results of Landiolol HCl 300 mg for Injection directly after reconstitution in 50 mL diluent (average of three determinations)

Tests	DP release specification limits*	L32103			L32104		
		WFI (release value)	0.9% NaCl	5% glucose	WFI (release value)	0.9% NaCl	5% glucose
pH	(b) (4)	6.7	6.6	6.4	6.7	6.6	6.5
Color and clarity		Complies	Complies	Complies	Complies	Complies	Complies
Osmolality		54	339	353	53	339	353

In addition, in response to CMC comments dated November 8, 2022, the Applicant provided comparative physicochemical data of Landiolol HCl 300 mg for Injection (listed as LDLL300) and Onoact® 50 after reconstitution with 0.9% NaCl and 5% Glucose (Table 5).

Table 5: Comparison of Physicochemical Parameters

	LDLL300	LDLL600	Onoact 50	LDL202
Parameters after reconstitution/dilution with NaCl				
pH	6,6	6,5	6,2	6,3
Osmolality (Osm/kg)	0,339	0,401	n.a.	1,896
Parameters after reconstitution/dilution with 5% Glucose				
pH	6,5	6,1	5.7	6,4
Osmolality (Osm/kg)	0,353	0,408	n.a.	1,918

n.a. not available

Assessment: {Adequate}

As shown in Table 5, AOP's proposed Landiolol HCl 300 mg for injection has similar pH (6.5-6.6) compared to that of the reconstituted Onoact® 50 (5.7-6.2) in NaCl or 5% Glucose. In addition, the reported pH values ((b) (4)) of reconstituted AOP's Landiolol HCl 300 mg for injection in WFI at 6 mg/mL in the original submission[3] are similar to the range of Onoact® 50 at 10 mg/mL (**Error! Reference source not found.**).

[3] \\CDSESUB1\EVSPROD\nda217202\0000\m3\32-body-data\32p-drug-prod\landiolol-hcl-injection-lyocontract\32p8-stab\stability-data.pdf

Table 6: Onoact Physical Form[2]

Brand Name	ONOACT for I.V. Infusion 50 mg	ONOACT for I.V. Infusion 150 mg
pH	5.5-6.5 (Solution prepared by adding 5 mL of water for injection to 1 vial of this product)	5.5-6.5 (Solution prepared by adding 15 mL of water for injection to 1 vial of this product)
Osmotic Pressure Ratio	Approx. 0.8 (Solution prepared by adding 2 mL of water for injection to 1 vial of this product)	Approx. 0.8 (Solution prepared by adding 6 mL of water for injection to 1 vial of this product)

Although the comparison of Osmolality is not available, the Applicant provided the following statement for the calculated Osmolality of Onoact® for injection[4]:

> While actual values for osmolality are not available for Onoact, the concentration of electrolytes is annotated with 0.092 mEq Chloride ions per vial, with trace amounts of sodium as pH regulator. This is in line with 50 mg Landiolol being present as hydrochloride salt per vial. In a standard dilution of 10 mg/ml active ingredient according to the label, Landiolol hydrochloride (546,06 g/mol) and mannitol (182,7 g/mol) account for about 92 mOsm/l to the total content of osmotically active particles present in the individual diluents. This puts Onoact between LDLL300 and LDLL600, as expected for a product with the same composition and a target concentration just below LDLL600 (10 mg/ml vs. 12 mg/ml). As noted above, the pH of reconstituted product largely depends on the batch of used diluent and has just limited informative value.

Drug Product Reviewer, Dr. Dan Berger, confirmed that the calculated osmolality of Diluted Onoact® at 10 mg/mL in saline is 400 mOsm/L (i.e.,92 mOsm/L +308 mOsm/L).

Therefore, the measured osmolality of reconstituted AOP's Landiolol HCl 300 mg for injection at 6 mg/mL in 0.9% NaCl or 5% Glucose (339 or 353 mOsm/kg) are considered comparable to reconstituted Onoact® 10 mg/mL and are within the acceptable clinical range (< 500 mOsmol/kg).

Primary Biopharmaceutics Assessor's Name and Date: Zhuojun Zhao, Ph.D., 2/14/2023

Secondary Assessor Name and Date: Haritha Mandula, Ph.D., 2/15/2023

[4] \\CDSESUB1\EVSPROD\nda217202\0013\m1\us\111-information-amendment\response-to-fda-quality-information-request.pdf

Zhuojun Zhao

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Haritha Mandula

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FDA U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	Indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
NDA Number	217202
Assessment Cycle Number	1
Drug Product Name / Strength	Landiolol hydrochloride for injection, 300 mg
Route of Administration	Intravenous Injection
Applicant Name	AOP Orphan Pharmaceuticals GmbH
Manufacturing Site	Lyocontract GmbH Pulverwiese 1 D-38871 Ilsenburg Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:

- This review covers sterility assurance and microbiological quality of the drug product.
- The product is (b) (4).

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
05/31/2022	05/31/2022	N/A	07/19/2022
08/03/2022	08/03/2022	N/A	
11/22/2022	11/22/2022	N/A	
1/25/2022	1/25/2022	N/A	

Remarks: An information request (IR) was conveyed on 07/21/2022 and a response was received from the applicant on 08/03/2022. A second IR was conveyed on 11/08/2022 and a response was received from the applicant on 11/22/2022. A follow-up IR was sent on 01/11/23. The response to all IRs is covered in this review.

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues:

Supporting Documents:

- D (b) (4) M19R01.docx dated 06/07/2022 referred for (b) (4) (b) (4)

Select Number of Approved Comparability Protocols: 00

S DRUG SUBSTANCE

Assessment: The drug substance (non-sterile, synthetic peptide) is (b) (4) (b) (4) of the drug product and the drug product is (b) (4). Therefore, microbiology review will not be conducted for drug substance.

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – Landiolol HCl 300 mg for injection is a white to almost white lyophilized powder in colorless 50 ml type (b) (4) glass vials closed with (b) (4) rubber stoppers, sealed with aluminum flip-off caps.

Name of ingredient	Quantity (per vial)	Function	Reference to Standards	% (w/v) Reconstituted solution	Concentration per mL Reconstituted solution

Landiolol hydrochloride (Landiolol)	300 mg (280 mg)	Active Pharmaceutical Ingredient	In-house specification	0.6	6 mg/mL
Mannitol (b) (4)	300 mg	(b) (4)	USP	0.6	6 mg/mL
Sodium hydroxide*	(b) (4)	pH adjustment	NF	(b) (4)	
Water for injection*	(b) (4)	(b) (4)	USP		

*Removed during lyophilization

- **Drug product composition** -
(3.2.P.1.)

Batch size:
The batch size of the validation batches is commercial production scale of (b) (4) kg (corresponding to (b) (4) L and a theoretical number of (b) (4) filled vials (b) (4) (b) (4)).

- **Description of container closure system (CCS)**
(3.2.P.7.)
A summary of the container closure system used for the Landiolol hydrochloride 300 mg for injection is shown in the table below:

Type	Description	Manufacturer
Glass vial	(b) (4) 50 njection vial, clear glass, Type (b) (4)	(b) (4)
(b) (4) rubber stopper	(b) (4) Grey, (b) (4) (b) (4)	
Flip off cap	20 mm crimp cap, Flip-off (b) (4) /Flip-off (b) (4) seal, (b) (4)	

Assessment: An adequate description of the drug product composition and container closure system was provided.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

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(b) (4)

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Assessment:

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES:

None

Primary Microbiology Assessor Name and Date:
Aditi Das, Ph.D., 1/31/2023

Secondary Assessor Name and Date:
Yuansha Chen, Ph.D., 1/31/2023

Aditi Das

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Yuansha Chen

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Theodore Carver

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