CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: November 14, 2024

To: Maryam Changi, Regulatory Project Manager
The Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for RAPIBLYK (landiolol) for injection, for intravenous use

NDA: 217202

Background:
In response to DCN's consult request dated July 3, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the resubmitted original NDA submission for RAPIBLYK (landiolol) for injection, for intravenous use.

PI
OPDP's review of the proposed PI is based on the draft labeling received via e-mail on November 7, 2024, 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 submitted by the sponsor to the electronic document room on November 8th and 13th, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
11/14/2024 01:00:00 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 13, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name, Dosage Form, and Strength:	Rapiblyk (landiolol hydrochloride) for injection, 280 mg/vial
Applicant Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
FDA Received Date:	November 13, 2024
TTT ID #:	2022-2280-5
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

AOP Orphan Pharmaceuticals GmbH (AOP) submitted revised container label received on November 13, 2024 for Rapiblyk. We reviewed the revised container label for Rapiblyk (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

AOP Orphan Pharmaceuticals GmbH implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Topper, C. Review of Revised Label and Labeling for Rapiblyk (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 NOV 08. TTT ID: 2022-2280-4.

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/s/

CHRISTINA A TOPPER
11/13/2024 08:37:14 PM

NICOLE F IVERSON
11/14/2024 12:49:42 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 8, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name, Dosage Form, and Strength:	Rapiblyk (landiolol hydrochloride) for injection, 280 mg/vial
Applicant Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
FDA Received Date:	November 8, 2024
TTT ID #:	2022-2280-4
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

AOP Orphan Pharmaceuticals GmbH (AOP) submitted revised container label and carton labeling received on November 8, 2024 for Rapiblyk. We reviewed the revised container label and carton labeling for Rapiblyk (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]

2 OVERALL ASSESSMENT

We performed a risk assessment of the revised container label and carton labeling for Rapiblyk to identify deficiencies that may lead to medication errors and other areas of improvement. We note that we were unable to assess if the established name is at least half the size of the proprietary name. To inform our review, the Agency sent an information request (IR) to the Applicant on November 6, 2024 via email communication stating:

> *"As currently presented, we are unable to assess if the established name is at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(22) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Please confirm that the established name is at least half the size of the established name in accordance with 21 CFR 201.10(g)(22)."*

The Applicant responded to the IR on November 8, 2024, confirming that the established name was half the size of the proprietary name[b].

3 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. We note that the linear barcode was removed from the container label and replaced with (b) (4) . The linear barcode is required on the container label. We provide recommendations for AOP in Section 4 below.

4 RECOMMENDATIONS FOR AOP ORPHAN PHARMACEUTICALS GMBH (AOP)

Container Label:

1. The linear barcode is required on the container label. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an

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[a] Topper, C. Review of Revised Label and Labeling for Rapiblyk (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 30. TTT ID: 2022-2280-3.

[b] Quality Information Amendment – Response to FDA Quality IR. Hillsborough (NC): AOP Orphan Pharmaceuticals GmbH; 2024 NOV 8. Available at: \\CDSESUB1\EVSPROD\nda217202\0041\m1\us\111-information-amendment\response-to-fda-quality-ir-dated-nov-01-2024.pdf

important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

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CHRISTINA A TOPPER
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NICOLE F IVERSON
11/08/2024 01:54:03 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 30, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name, Dosage Form, and Strength:	Rapiblyk (landiolol hydrochloride) for injection, 280 mg/vial
Applicant Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
FDA Received Date:	October 24, 2024
TTT ID #:	2022-2280-3
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

AOP Orphan Pharmaceuticals GmbH (AOP) submitted revised container label and carton labeling received on October 24, 2024 for Rapiblyk. We reviewed the revised container label and carton labeling for Rapiblyk (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]

2 OVERALL ASSESSMENT

We performed a risk assessment of the revised container label and carton labeling for Rapiblyk to identify deficiencies that may lead to medication errors and other areas of improvement.

On October 29, 2024, we consulted with the Office of Pharmaceutical Quality (OPQ) to confirm whether the presentation of the dosage form, "for injection" was correct or if it should be presented with a capital "I" to read "for Injection". OPQ confirmed that the dosage form should be revised and had already finalized their review. Therefore, DMEPA agreed to send the recommendation regarding the dosage form to the Applicant.

3 CONCLUSION

The container label and carton labeling is unacceptable from a medication error perspective. We note (b) (4) are utilized for the proprietary name, which may lead to misinterpretation of the proprietary name. We provide recommendations for AOP in Section 3 below.

4 RECOMMENDATIONS FOR AOP ORPHAN PHARMACEUTICALS GMBH (AOP)

A. General Comments (Container Label and Carton Labeling)

1. The proprietary name, Rapiblyk, is presented (b) (4) for the entire proprietary name in order to improve readability and avoid misinterpretation of the proprietary name.
2. As currently presented, the dosage form is represented as "for injection" on the proposed container label and carton labeling. The proposed dosage form "for injection" is inconsistent with USP General Chapter <7> labeling[b] and USP General Chapter <1121> Nomenclature[c] in which the letter "i" at the beginning of the word "injection" is capitalized. The Office of Pharmaceutical Quality

[a] Topper, C. Label and Labeling Review for Rapiblyk (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 19. TTT ID: 2022-2280-2.

[b] United States Pharmacopoeia (USP) General Chapter <7> Labeling. Available from http://app.uspnf.com/uspnf/pub/index?usp=40&nf=35&s=2&officialOn=December 1, 2017.

[c] United States Pharmacopoeia (USP) General Chapter <1121> Nomenclature. Available from http://app.uspnf.com/uspnf/pub/index?usp=40&nf=35&s=2&officialOn=December 1, 2017.

(OPQ) has confirmed that the dosage form should appear as “for Injection”. As such, revise the dosage form from “for injection” to “for Injection” in accordance with USP General Chapter <1121> Nomenclature.

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/s/

CHRISTINA A TOPPER
10/30/2024 10:59:45 AM

NICOLE F IVERSON
10/30/2024 05:04:48 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 19, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name, Dosage Form, and Strength:	Rapiblyk (landiolol hydrochloride) for injection, 280 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
FDA Received Date:	May 29, 2024 and June 6, 2024
TTT ID #:	2022-2280
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

This is a corrected review that does not change the overall conclusions of the original review dated September 19, 2024.

1 INTRODUCTION

As part of the approval process of the 505(b)(2) NDA class II resubmission for Rapiblyk for injection, we reviewed the proposed Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Landiolol is a proposed 505(b)(2) drug product, relying on published literature describing a non-US approved landiolol HCl product.

DMEPA previously reviewed the prescribing information (PI), container label, and carton labeling for landiolol under NDA 217202.[a]

1.2 REGULATORY HISTORY

AOP Orphan Pharmaceuticals GmbH (AOP) previously submitted NDA 217202 on May 31, 2022. We completed a label and labeling review on January 25, 2023[a]. Our container label and carton labeling recommendation were provided to AOP on February 23, 2023. In addition, our recommendations for the PI were provided to AOP on February 23, 2023.

AOP submitted revised label and labeling on March 15, 2023 and we completed a label and labeling memo on March 28, 2023. AOP submitted revised label and labeling on April 12, 2023. However, the application received a Complete Response letter on May 31, 2023 due to product quality and manufacturing issues.[b]

Thus, AOP Orphan Pharmaceuticals GmbH (AOP) submitted a Class 2 Resubmission on May 29, 2024.[c]

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 217202.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

[a] Myers, D. Label and Labeling Review for landiolol (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JAN 25. TTT ID No.: 2022-2280.

[b] Changi, M on behalf of Hylton V. Joffe. Complete Response for NDA 217202. Silver Spring (MD): FDA, CDER, OND, Division of Cardiology and Nephrology (DCN) (US); 2023 MAY 31. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806d0ffc

[c] Resubmission Response for NDA 217202 landiolol. Vienna (Austria): AOP Orphan Pharmaceuticals GmbH (AOP); 2024 MAY 29. Available from: \\CDSESUB1\EVSPROD\nda217202\0032\m1\us\12-cover-letters\cover-letter.pdf.

3 OVERALL ASSESSMENT

We performed a risk assessment of the proposed Prescribing Information (PI), container label, and carton labeling for Rapiblyk to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the labeling for Rapiblyk is proposed in mg, which is incongruous with the dosing (mcg/kg/min). While we generally discourage the labeling of a product in units that are incongruent with the dosing instructions, we note that other titratable medications used in the acute care setting follow this pattern (e.g., epinephrine for hypotensive shock is labeled in mg and dosed in mcg) and that using larger numbers may convey additional safety risks due to misinterpretation of large numbers (i.e., 280 mg is equivalent to 280,000 mcg). Therefore, in this case, we agree with labeling the product in mg and dosing in mcg/kg/min.

We also note that the container label and carton labeling include the following statements: "Keep out of the sight and reach of children." And "No preservative", however, these statements were not included in Section 16 of the PI.

We consulted with the Office of Pharmaceutical Quality (OPQ) via email communication on September 5, 2024, to determine if it is appropriate to include the statements "Keep out of the sight and reach of children" and "No preservative" in the PI. OPQ responded on September 5, 2024, via email stating that it is appropriate to include these statements in the PI. OPQ also recommended adding a comment that the product is sterile in Section 16 of the PI as well as the container label and carton labeling.

We further note for the container label and carton labeling that the product strength is located between the established name and dosage form. For NDAs, the finished dosage form should be present and located either in the same line as the active ingredient or directly below the active ingredient. We consulted with OPQ via email communication on September 10, 2024, to determine if it was appropriate to revise the dosage form location. OPQ responded on September 10, 2024, via email in agreement and stated they would send an information request to the Applicant recommending this revision. Additionally, after further discussion via email, OPQ retracted their recommendation to add the comment regarding the product being sterile to Section 16 of the PI as well as the container label and carton labeling.

4 CONCLUSION

The proposed Rapiblyk Prescribing Information (PI), container label, and carton labeling may be improved to promote 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 for the Division of Cardiology and Nephrology (DCN) in Section 4 and for AOP Orphan Pharmaceuticals GmbH (AOP) in Section 5.

5 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. General Comments (Highlights of Prescribing Information and Full Prescribing Information)

1. As currently presented, the proprietary name is denoted by the placeholder "BRANDNAME" in the highlights of prescribing information and full prescribing information. We reference our August 27, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Rapiblyk, was found conditionally acceptable. Therefore, we recommend replacing the placeholder "BRANDNAME" with the conditionally acceptable proprietary name, Rapiblyk.

B. Highlights of Prescribing Information (HPI)

1. Dosage and Administration

a. The route of administration is described as (b) (4), which does not specify how to administer the product (b) (4). This lack of information may lead to wrong technique drug administration errors. We recommend revising the route (b) (4) to "intravenous infusion" to minimize the risk of the product being administered as an intravenous bolus.

C. Full Prescribing Information

1. Section 2 Dosage and Administration

a. As currently presented, the reference in the last bullet point under subsection 2.4 *Instructions for Preparation* references Table 3, which represents the (b) (4). However, the reconstituted solution storage and use conditions are in Table 2. For clarity, revise the last bullet to read "Use immediately. The reconstituted BRANDNAME solution storage conditions are described in Table 2."

b. As currently presented, section 2.5 *Administration* contains the abbreviation "h". Error prone abbreviations may lead to misinterpretation and medication error. For clarity, we recommend replacing the abbreviation "h" with the intended meaning, "hour".

c. (b) (4)

2. Section 16 How Supplied/Storage and Handling

    a. As currently presented, the container label and carton labeling indicate that the product is "preservative-free"; however this information is missing from the PI, which that may lead to confusion on how to handle the product. The Office of Pharmaceutical Quality (OPQ) has confirmed that the statement, "preservative-free" should be included in the PI to be consistent with the container label and carton labeling. We recommend revising the statement "BRANDNAME is supplied as a white to almost white lyophilized powder in single dose vials containing 280 mg landiolol for injection." to "BRANDNAME is supplied as white to almost white, preservative-free, lyophilized powder in single dose vials containing 280 mg landiolol for injection."

    b. The storage statement can be improved for clarity and consistency with the carton labeling. Specifically, we recommend adding the statement "Keep out of the sight and reach of children."

6 RECOMMENDATIONS FOR AOP ORPHAN PHARMACEUTICALS GMBH (AOP)

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholder "Tradename". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our August 27, 2024, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Rapiblyk, was found conditionally acceptable. We recommend replacing the placeholder "Tradename" with the conditionally acceptable proprietary name, Rapiblyk, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. The established name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you

intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

4. The "Rx only" statement appears more prominent than other critical information (e.g., route of administration) on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

5. As currently presented, there are no instructions on the PDP to indicate that the product must be reconstituted and further diluted for intravenous infusion. This lack of information may lead to wrong preparation errors. We recommend including a statement on the principal display panel to indicate that the product must be reconstituted and further diluted prior to administration. For example, revise (b) (4) to "For intravenous infusion after reconstitution".

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 1 presents relevant product information for Rapiblyk received on June 6, 2024 from AOP Orphan Pharmaceuticals GmbH (AOP).

Table 1. Relevant Product Information for Rapiblyk	
Initial Approval Date	N/A
Active Ingredient	landiolol hydrochloride
Indication	A beta-1 adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Dosage Form	for injection
Strength	280 mg/vial
Route of Administration	Intravenous
Dose and Frequency	For patients with normal cardiac function, titrate using ventricular rate at 10-minute intervals • (b) (4) • (b) (4) start at 10 mcg per kg per minute; adjust dose as needed up to 40 mcg per kg per minute in 10 mcg per kg per minute increments to achieve desired reduction of ventricular rate. For patients with impaired cardiac function (b) (4) titrate using ventricular rate at 15-minute intervals • Start at 1 mcg per kg per min, adjust dose as needed up to (b) (4) mcg per kg per min in 1 mcg per kg per min increments to achieve desired reduction of ventricular rate.
How Supplied	BRANDNAME is supplied as a white to almost white lyophilized powder in single dose vials containing 280 mg landiolol for injection. (equivalent to 300 mg landiolol HCl). Each vial is supplied in a carton NDC xxxxx-xx-xx
Storage	Store unreconstituted product at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature], with excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Landiolol HCl 300 mg for injection is a lyophilized powder in colorless glass vials of 50 ml. The vials are closed with a (b) (4) rubber stopper and sealed with an aluminum flip-off cap.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Rapiblyk labels and labeling submitted by AOP Orphan Pharmaceuticals GmbH (AOP).

- Prescribing Information received on June 6, 2024, available from \\CDSESUB1\EVSPROD\nda217202\0033\m1\us\114-labeling\draft\labeling\draft-labelling-text_track.pdf
- Container label received on June 06, 2024
- Carton labeling received on June 06, 2024

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On July 15, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'NDA 217202' and 'landiolol'. Our search identified two previous review(s)[e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Myers, D. Label and Labeling Review for landiolol (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JAN 25. TTT ID No.: 2022-2280.

[f] Myers, D. Label and Labeling Review Memo for landiolol (NDA 217202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 27. TTT ID No.: 2022-2280-1.

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/s/

CHRISTINA A TOPPER
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NICOLE F IVERSON
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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: May 30, 2023

To: Maryam Changi, Regulatory Project Manager
The Division of Cardiology and Nephrology (DCN)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for Landiolol HCL

NDA: 217202

This memo is in response to DCN's labeling consult request dated August 8, 2022. OPDP defers comment on the proposed labeling at this time, and requests that DCN submit a new consult request during the subsequent review cycle. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
05/30/2023 11:19:28 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Date of Consult Request:	April 12, 2023
From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatrics and Maternal Health (DPMH)
Through	Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH, and Lynne Yao, MD, Division Director, DPMH
To:	Division of Cardiology and Nephrology (DCN)
NDA Number:	217202
Drug:	Landiolol HCL for injection, for intravenous use.
Applicant:	AOP Orphan Pharmaceuticals GmbH
Indication:	Indicated for the short-term treatment reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter
Subject:	Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Materials Reviewed

- Applicant's submission of May 31, 2022
- Division's Consult request of October 26, 2022, in DARRTS and Reference ID: 5066930
- Applicant's response of December 2, 2022 to the Information Request (IR) of November 3, 2022 submitted by the Division.

INTRODUCTION

On May 21, 2022, the applicant, AOP Orphan Pharmaceuticals GmbH (AOP) submitted this NDA 217202 under the 505(b)(2) pathway of the Food, Drug and Cosmetic Act for landiolol for the short-term treatment reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. Landiolol is to be administered intravenously, in a hospital setting (emergency department, perioperatively, in the operating room, in the intensive care unit) or in an acute care setting. DCN has requested DPMH to ensure that the landiolol labeling complies with the PLLR content and format.

BACKGROUND

Regulatory History

As per the DCN RPM filling review, under Chemical Classification, this application is considered Type 1- New molecular Entity (NME) and Type of original NDA: 505(b)(2). This application is submitted as a 505(b)(2) and is depending on published literature. The applicant has not conducted any studies. They have bridged the current formulation to Onoact.
The landiolol hydrochloride product is approved outside the USA (Rapibloc with EMA decision date April 16, 2021, Onoact with Japan March 26, 2019) and indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.

Arrhythmias and Pregnancy[1]

Arrhythmias are the most common cardiac conditions encountered during pregnancy in females with and without structural heart disease.[1,2] In the United States, an analysis of a hospital discharge diagnosis database demonstrated the incidence of pregnancy-related hospitalizations with arrhythmias has increased between 2000 and 2012 primarily due to increases in the incidence of atrial fibrillation (111% increase; from 18 per 100 000 to 35 per 100 000) and ventricular tachycardia (127% increase; from 10 per 100 000 to 21 per 100 000), while SVT was relatively stable (12% increase).[3] Arrhythmias may appear for the first time during pregnancy. Pregnancy may also cause an exacerbation in those patients with pre-existing arrhythmias.[4,5] The exact mechanism of developing arrhythmias during pregnancy is unclear but contributing factors are considered to be hemodynamic, hormonal, and autonomic changes related to pregnancy. The hemodynamic changes of pregnancy have been studied, and likely contribute to the development of arrhythmias during pregnancy.[6] There is also an increase in resting heart rate, which has been associated with markers of arrhythmogenesis such as late potentials, premature ventricular contractions, and depressed heart

[1] Uptodate: Supraventricular arrhythmias during pregnancy. Last updated January 31, 2022
[2] Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001; 104:515.
[3] Vaidya VR, Arora S, Patel N, et al. Burden of Arrhythmia in Pregnancy. Circulation 2017; 135:619.
[4] Lee SH, Chen SA, Wu TJ, et al. Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 1995; 76:675.
[5] Silversides CK, Harris L, Haberer K, et al. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. Am J Cardiol 2006; 97:1206.
[6] Silversides CK, Colman JM. Physiological changes in pregnancy. In: Heart disease in pregnancy, 2nd ed, Oakley C, Warnes CA (Eds), Blackwell Publishing, Malden 2007. p.6.

rate variability.[7,8]
Focal atrial tachycardia is relatively rare during pregnancy. Although this arrhythmia is often associated with structural heart disease in nonpregnant patients, most reports of atrial tachycardia during pregnancy have been reported in patients without apparent structural heart disease.[9,10]
Amongst arrhythmias during pregnancy, atrial fibrillation (AF) has had the greatest recent increase in incidence.[3] Advancing maternal age and higher burden of AF risk factors (hypertension, diabetes mellitus, obesity, and congenital heart disease) explain increased atrial fibrillation rates. Although atrial fibrillation and flutter can occur in pregnant patients with structurally normal hearts,[11] they are more common in pregnant patients with structural heart disease, such as rheumatic heart disease, valvular heart disease, hypertrophic cardiomyopathy,[12] peripartum cardiomyopathy, and congenital heart disease.[13,14]

Treatment of arrhythmias in pregnant and non-pregnant patients are similar; however, treatment in pregnancy is warranted when symptoms are clinically significant, or the patient is hemodynamically unstable. An arrhythmia is considered hemodynamically unstable, if aortic pressure decreases by ≥15mmHg, marginally unstable, if pressure decrease by 5-15mmHg and hemodynamically stable if pressure increases or decreases no more than 5mmHg. [15] In the inpatient setting, perfusion status is a primary consideration in arrhythmia management.[16] Hemodynamically stable or unstable arrhythmia depends on multiple factors, such as volume status, medications, autonomic tone, and degree of cardiac ischemia. Medications used intravenously for supraventricular arrhythmias include beta selective blockers (propranolol hydrochloride, metoprolol, sotalol injection, esmolol injection, nebivolol), verapamil and digoxin.

[7] Kamkin A, Kiseleva I, Isenberg G. Stretch-activated currents in ventricular myocytes: amplitude and arrhythmogenic effects increase with hypertrophy. Cardiovasc Res 2000; 48:409.
[8] Soliman EZ, Elsalam MA, Li Y. The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording. Europace 2010; 12:261.
[9] Shotan A, Ostrzega E, Mehra A, et al. Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. Am J Cardiol 1997; 79:1061.
[10] Murphy JJ, Hutchon DJ. Incessant atrial tachycardia accelerated by pregnancy. Br Heart J 1992; 68:342.
[11] Kuczkowski KM. New onset transient lone atrial fibrillation in a healthy parturient: déjà vu. Int J Cardiol 2004; 97:339.
[12] Autore C, Conte MR, Piccininno M, et al. Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol 2002; 40:1864.
[13] Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation 2007; 115:534.
[14] Tateno S, Niwa K, Nakazawa M, et al. Arrhythmia and conduction disturbances in patients with congenital heart disease during pregnancy: multicenter study. Circ J 2003; 67:992.
[15] Turcott, RG and Pavek, TJ Identification of Hemodynamically Unstable Arrhythmias Using Subcutaneous Photoplethysmography J Cardiovasc Electrophysiol. 2010 Apr; 21(4): 448–454. Published online 2009 Oct 20.
[16] 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005;112:IV1–IV203.

Drug Characteristics[17]

Half Life	4 min
Molecular Weight	546.06 g/mol
Protein bound	<10%
Dosing	Landiolol is to be infused for up to 24 hours
Dose	**Normal cardiac function:** (b) (4) (b) (4) start at 10 mcg per kg per minute; adjust dose as needed up to 40 mcg per kg per minute in 10 mcg per kg per minute increments to achieve desired reduction of ventricular rate. **Impaired cardiac function** (b) (4) : Start at 1 mcg per kg per min, adjust dose as needed up to (b) (4) mcg per kg per min in 1 mcg per kg per min increments to achieve desired reduction of ventricular rate.

Mechanism of action: Landiolol is a selective beta-1-adrenoreceptor antagonist (the selectivity for beta-1-receptor blockade is 255-times higher than for beta-2-receptor blockade) that inhibits the positive chronotropic effects of the catecholamines adrenaline and noradrenaline on the heart, where beta-1-receptors are predominantly located. At therapeutic dosages, landiolol does not exhibit any membrane-stabilizing activity or intrinsic sympathomimetic activity in vitro.

REVIEW

Pregnancy

Non Clinical Data

As per the applicant, investigation of landiolol in pregnant rats showed distribution of landiolol to the placenta and the fetus. In animal reproduction studies, no embryo-fetal developmental toxicity was observed in rats and rabbits during the period of organogenesis at landiolol exposure (AUC) in rats approximately 2.7-times higher than human exposure at the maximum recommended human dose (MRHD). In rabbits, the resulting systemic landiolol exposure at the highest dose level was not determined. In a rat study, no effect on pre/post-natal development was observed at landiolol exposures approximately 5.4-times higher than human exposure at the MRHD.

Clinical Data

Applicant's Review of Literature

The applicant conducted a review of the available published literature on PubMed, J-Stage, CiNii, and Google Scholar regarding Landiolol use in pregnant women. They identified only one publication by Suehiro K and Okutani, 2012[18] where landiolol was administered to women at the time of anesthesia induction for cesarean section. Sixty-four patients were randomized. Thirty-two patients were administered, in addition to other anesthetics, a single dose of landiolol 0.2 mg/kg; and

[17] Landiolol proposed labeling as of May 31, 2022

[18] Suehiro Koichi and Ryu Okutani, Landiolol attenuates cardiovascular response at induction of general anesthesia for cesarean delivery. J Anesth, 2012 Apr;26(2):200-5. Epub 2011 Dec 17.

32 patients did not get landiolol, no other beta-blockers were used in these patients, but they received the same anesthetics. The authors observed significantly lower percentage changes in BP and HR ($p < 0.05$ each) in the patients who took landiolol vs the control. Intraoperative blood loss, frequency of decreased uterine contraction, and fetal Apgar scores did not differ significantly between groups. The authors concluded that landiolol provides adequate hemodynamic regulation during general anesthesia induction in patients undergoing cesarean delivery.

Reviewer Comment

In Suehiro K and Okutani, 2012, the fetal heart rate (FHR) was monitored as soon as patients entered the operating room. From before starting anesthesia to the time of delivery, FHR and need for additional treatment with uterotonic or vasopressor agents, and neonatal Apgar scores were recorded. Intraoperative blood loss, frequency of decreased uterine contraction, FHR and neonatal Apgar scores did not differ significantly between patients who took landiolol vs those who did not. Limitations of this study include small numbers of patients (32 in each group) and all pregnancies were with healthy mothers (no cardiovascular risk factors were reported) and fetuses. No major congenital malformations were reported. No confounders are described.

DPMH Review of Literature

DPMH searched PubMed, Reprotox and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation for use of landiolol during pregnancy. No publications were identified.

What Is Known About Safety with Other Beta-Blockers During Pregnancy

Beta-blockers have been demonstrated to cross the placenta. Esmolol crosses the placenta during the fetal stage in sheep, but fetal concentrations were only 8% of maternal concentrations and was not teratogenic. Metoprolol has not demonstrated an association of adverse developmental outcomes with maternal use of metoprolol during pregnancy. Metoprolol crosses the placenta in humans and maternal and fetal blood concentrations are about equal. Sotalol crosses the placenta and was found in amniotic fluid. Beta-blockers cross the placenta and potentially can cause physiological changes in the fetus.[19,20] Beta Blocker exposure has been shown to cause bradycardia and hypoglycemia in the neonate.[21] The published literature has also reported inconsistent findings of intrauterine growth retardation, preterm birth, and perinatal mortality with maternal use of beta-blockers (metoprolol) during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These data cannot definitively establish or exclude any drug-associated risk during pregnancy.

Summary

Landiolol is a selective beta-1-adrenoreceptor antagonist. It crosses the placenta during the fetal stage in rats. There are no human data available with use of landiolol during pregnancy, except the above published study in which no adverse events were reported in fetuses or neonates. Treatment should not be withheld from pregnant patients who require the medication.

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[19] Lewei Duan, MS1; Angie Ng, MD2; Wansu Chen, PhD1; et al. β-Blocker Exposure in Pregnancy and Risk of Fetal Cardiac Anomalies. JAMA Intern Med. 2017;177(6):885-887

[20] Davis RL, Eastman D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to calcium channel and beta-blockers during pregnancy. Pharmacoepidemiol Drug Saf. 2011;20(2):138-145.

[21] Bateman BT, Patorno E, Desai RJ, et al. Late pregnancy β blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics. 2016;138(3):e20160731.

Reviewer Comment

The applicant proposed to use in the Subsection 8.1. Pregnancy, Risk Summary "In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 3%" using as justification "the CDC web page for statistics on US birth defects (https://www.cdc.gov/ncbddd/ birthdefects/data.html)." DPMH acknowledges the 2008 CDC reference provided, however, it is limited to the metropolitan Atlanta area. We consider various population-based data sources/publications (including Texas Birth Defects Registry, March of Dimes, CDC, Mai CT et al. 2019, etc.) used to estimate the overall prevalence of major birth defects. Because there is no single comprehensive birth defect surveillance program in the United States, various population-based data sources have been used to estimate the overall prevalence of major birth defects, including the Metropolitan Atlanta Congenital Defects Program and the Texas Birth Defects Registry. These programs vary in methods of ascertainment and goals and objectives. Additional factors that may affect the birth defect rate include, but are not limited to, certain medical conditions, maternal age, race, ethnicity, and gestational age. The Centers for Disease Control and Prevention (CDC) reports a major birth defect rate of approximately 3 percent based on pooled data from state-based programs across the United States. These data serve to estimate national rates, indicate regional variations, and describe the epidemiology of specific birth defects. Because various factors may affect the overall major birth defect rate, FDA believes a range of 2 to 4 percent is a reasonable representation of the background major birth defect rate. Therefore, we recommend to maintain the Agency revision to 2-4% for background risk of major birth defects in the general US population.

Lactation

Non Clinical and Clinical Data

No relevant nonclinical or clinical information for landiolol use during lactation was identified by either the applicant or by this reviewer.

Landiolol has a small molecular weight and low protein binding (<10%). It was excreted in the rat milk corresponding to approximately 70% of the concentration in rat plasma. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The concentration of landiolol in animal milk does not necessarily predict the concentration of drug in human milk.

What is Known About Safety with Other Beta-Blockers during Lactation

No pediatric concerns have been reported via exposure in breast milk from other beta-blockers over the years. Based on physicochemical properties, poor oral availability, and extremely short half-life, i.e., esmolol, would not be expected to cause any adverse effects in breastfed infants. Relative infant exposure to metoprolol through breast milk in one study was <1.0% of maternal weight-adjusted dose. Metoprolol is present in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug.

Summary

Because landiolol administration is in an acute setting, the capability for a patient to breastfeed would be based on the physician's determination of benefit/risk. Landiolol would likely clear the patient's systemic circulation in 25 minutes following the end of infusion. Therefore, the risk/benefit statement should be included in the labeling stating "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRANDNAME and any potential adverse effects on the breast fed infant from BRANDNAME or from the underlying maternal condition.

Females and Males of Reproductive Potential

Non Clinical and Clinical Data

No relevant published information was identified by either the applicant or this reviewer for landiolol use in patients of reproductive potential. No adverse effects on fertility were observed in male and female rats at

a landiolol dose of 100 mg/kg/day, resulting in systemic exposure (AUC) approximately 10-times the exposure at the MRHD. Use of Landiolol in an acute setting and for up to 24 hours, is not expected to have any impact on erectile dysfunction or sperm motility. Therefore, because landiolol does not have any reported effects on fertility, it is not teratogenic (it is not genotoxic in different assays), and there is no need for pregnancy testing or contraception recommendations, subsection 8.3 Females and Males of Reproductive Potential will be omitted from the labeling.

Summary of What is Known About Safety with Other Beta-Blockers

Based on the published literature, beta-blockers (metoprolol) may cause erectile dysfunction and inhibit sperm motility if used in the long term. Not all beta-blockers have the same effects on erectile function and sperm motility as it is evident from the respective labelings. In animal fertility studies, metoprolol has been associated with reversible adverse effects on spermatogenesis starting at oral dose level of 3.5 mg/kg in rats, which would correspond to a dose of 34 mg/kg/day in humans in mg/m2 equivalent, although other studies have shown no effect of metoprolol on reproductive performance in male rats. No evidence of impaired fertility due to metoprolol was observed in rats.

CONCLUSION

The available clinical data is insufficient to determine whether Landiolol is teratogenic. In animal reproduction studies, no embryo-fetal developmental toxicity was observed in rats and rabbits during the period of organogenesis at landiolol exposure (AUC) in rats approximately 2.7-times higher than human exposure at the maximum recommended human dose (MRHD). In a rat study, no effect on pre/post-natal development was observed at landiolol exposures approximately 5.4-times higher than human exposure at the MRHD. Landiolol was not genotoxic when tested in a battery of assays. There are no animal or human safety signals.

Landiolol is a short acting beta 1 blocker. Treatment should not be withheld from pregnant patients who require this medication for a supraventricular arrhythmia. It crosses the placenta during the fetal stage in rats. Therefore, it may theoretically produce signs of beta blockade in the fetus after treatment of the mother. Neonates born to mothers who are receiving landiolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Neonates should be monitored when they were exposed to landiolol during pregnancy and labor for hypotension, hypoglycemia, bradycardia, and respiratory depression and be manage accordingly. The short half-life of landiolol suggests that the breastfed infant's exposure to the drug will be limited. Also, because of theoretical concerns, the breastfed infant should be monitored for bradycardia and other symptoms of beta blockade such as lethargy (hypoglycemia). The capability for a patient to breastfeed would be based on the physician's determination of benefit/risk.

DPMH does not recommend pregnancy or lactation post-marketing requirement (PMR) studies because landiolol is indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia, including atrial fibrillation and atrial flutter (usually older adults). Landiolol would be used short-term while in the hospital setting where patients may not be aware of what drugs they are receiving. Experience with other intravenously administered beta-blockers for longer durations have not suggested any serious adverse reactions to the fetus over the years. However, it has been found for some beta-blockers that they may cause bradycardia and hypoglycemia in the neonate when they are administered close to delivery. For other beta-blockers, they may only theoretically produce signs of beta blockade in the fetus after treatment of the mother. Routine pharmacovigilance should capture any new cases of use of landiolol during pregnancy.

DPMH revised subsections 8.1 and 8.2 of landiolol labeling for compliance with the PLLR (see below). Labeling recommendations reflect input from Nonclinical reviewers. DPMH refers to the

final NDA action for final labeling.

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04/18/2023 05:24:07 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	March 27, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name, Dosage Form, and Strength:	landiolol for Injection, 280 mg/vial
Applicant/Sponsor Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
TTT ID #:	2022-2280-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 15, 2023 for landiolol. The Division of Cardiology and Nephrology (DCN) requested that we review the revised container label and carton labeling for landiolol (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]

2 CONCLUSION

The revised container label and carton labeling is unacceptable 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 3 (Table 1) for AOP Orphan Pharmaceuticals GmbH.

3 RECOMMENDATIONS FOR AOP ORPHAN PHARMACEUTICALS GMBH

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

[a] Myers, D. Label and Labeling Review for landiolol (AOP Orphan Pharmaceuticals GmbH). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JAN 25. TTT ID No.: 2022-2280.

Table 1. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	Placement of the graphic and use of (b) (4) for the proprietary name can lead to misinterpretation.	"The use of logos, stripes, watermark graphics, lines, and symbols on container labels and/or carton labeling may help to differentiate products, but it should not distract the reader from critical information or add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort critical information." "We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name because the logo can look like an additional letter in the proprietary name."[b]	To prevent misinterpretation of the proprietary name, we recommend decreasing the prominence of the graphic away from the proprietary name.
2.	As currently presented, the established name on the PDP lacks prominence commensurate with the proprietary name and is not at least half the size of the proprietary name.	Per 21 CFR 201.10 (g)(2): *"The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name..."*[c]	Revise the established name to be in accordance with 21 CFR 201.10 (g)(2).
3.	As currently presented, the route of	Lack of prominent display of the route of	We recommend moving the route of administration (b) (4)

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.
[c] 21 CFR 201.10(g)(2).

Table 1. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	administration is not prominent on the principal display panel.	administration may cause confusion.	(b) (4) to above the "Single-dose vial" statement to increase its prominence and prevent confusion.
Container Label			
1.	As currently presented, the product strength is "280 mg" which could lead to confusion.	For dry solid injectable products requiring reconstitution the strength should be expressed in terms of the quantity of drug per vial (e.g., XX mg/vial or XX mg per vial).[d]	To minimize confusion, revise all occurrences of the current strength expression "280 mg" to instead "280 mg/vial" or "280 mg per vial."
2.	As currently presented, the information on the side panel is repetitive and lacks readability.	Presenting information in this manner may cause confusion.	We recommend removing the statement "(b) (4) See prescribing information.". We recommend removing the "Discard unused portion." statement from the side panel as the statement is already present on the principal display panel.
3.	As currently presented, there is a (b) (4) statement that is not needed as it contains information already present in other areas of the principal display panel.	Presenting duplicative information may hinder the readability of other important information on the label.	We recommend removing the duplicative statement (b) (4) as it is not needed.
Carton Labeling			

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

Table 1. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, there is redundant information as part of the net quantity statement (e.g., (b) (4)).	Lack of clarity in the net quantity statement may cause confusion.	We recommend revising the net quantity statement to “One Vial”.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	January 25, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217202
Product Name and Strength:	landiolol[a] for Injection, 280 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AOP Orphan Pharmaceuticals GmbH (AOP)
FDA Received Date:	May 31, 2022, December 19, 2022, and January 03, 2023
TTT ID #:	2022-2280
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[a] Labels and labeling submitted by the Applicant for NDA 217202 includes the previously proposed proprietary name, (b) (4), which was denied on October 06, 2022. A proprietary name has not been found conditionally acceptable at this time. Thus, the established name, landiolol, will be used for this Label and Labeling review.

1 REASON FOR REVIEW

As part of the approval process for landiolol for Injection, a 505(b)(2) referencing Esmolol, we reviewed the proposed prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION AND RECOMMENDATIONS

We performed a risk assessment of the proposed prescribing information (PI), container label, and carton labeling to determine if they are acceptable from a medication error perspective. We note the product should be prepared by reconstituting with 50 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection (b) (4)

[redacted]

[b] Changi, M. FDA Communication: New Information request NDA 217202. Silver Spring (MD): FDA, CDER, OND, DCN (US); 2022 DEC 13. NDA 217202. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806a204e.

(b) (4)

In addition, we note that on January 3, 2023, AOP Orphan Pharmaceuticals submitted revised labeling which included revision to the strength (from 300 mg/vial to 280 mg/vial) and dosing (from 1 mcg/kg/min to (b) (4) mcg/kg/min) in response to an information request from Office of Pharmaceutical Quality.

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

4 RECOMMEDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

Table 2. Identified Issues and Recommendations for Division of Cardiology and Nephrology (DCN)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented under the "*Dosage Forms and Strengths*" header, the product is described as "(b) (4)	Inclusion of the (b) (4) may be misinterpreted (b) (4).	To minimize the potential for misinterpretation, remove the text (b) (4) For example, "For injection: 280 mg of landiolol as a lyophilized powder in a single-dose vial."
Full Prescribing Information (FPI) – Section 2 *Dosage and Administration*			
1.	As currently presented, we note the inclusion of the use of the error-prone abbreviation "IV" in subsections 2.1 *Dosing*	Abbreviations can be a source of misinterpretation and result in error.[c]	Delete the occurrences of the abbreviation "IV" within subsections 2.1 and 2.2.

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

Table 2. Identified Issues and Recommendations for Division of Cardiology and Nephrology (DCN)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	for Patients with Normal Cardiac Function and 2.2 *Dosing for Patients with Impaired Cardiac Function* (b) (4) (i.e., "BRANDNAME is administered as a continuous intravenous (IV) infusion…").		For example, "BRANDNAME is administered as a continuous intravenous infusion…")
2.	As currently presented, subsection (b) (4) states to (b) (4)	We note that there are no further directions currently included in subsection (b) (4) regarding further diluting the reconstituted product (b) (4)	To provide clarity and prevent wrong technique and/or product preparation errors, including wrong product concentration medication errors, we recommend revising as follows:

Table 2. Identified Issues and Recommendations for Division of Cardiology and Nephrology (DCN)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			• Use appropriate aseptic technique for reconstitution. • 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. • Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be a clear, colorless solution. • Use immediately. The reconstituted BRANDNAME solution storage conditions are described in Table 3. • Discard unused portion.
3.	As currently presented, in subsection (b) (4) does not include appropriate standard nomenclature for the diluents (i.e., (b) (4)	Use of not appropriate standard nomenclature may contribute to confusion that can result in potential mediation error.	For consistency and clarity, we recommend revising the current text "(b) (4) (b) (4) to instead "0.9% Sodium Chloride Injection, USP" and (b) (4) (b) (4)" to instead "5% Dextrose Injection, USP."

Table 2. Identified Issues and Recommendations for Division of Cardiology and Nephrology (DCN)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	As currently presented, the product is described as "... (b) (4) (b) (4)"	Inclusion of the (b) (4) (b) (4) may be misinterpreted (b) (4) .	To minimize the potential for misinterpretation, remove the text (b) (4) For example, For injection: 280 mg of landiolol as a lyophilized powder in a single-dose vial."
Full Prescribing Information – Section 11 *Description*			
1.	As currently presented in Section 11, "*Description*", the product is described as "...in a 50 mL vial." Additionally, as currently presented, a package type term, (i.e., "single-dose") is not included prior to the first occurrence of the word "vial."	(b) (4)(4) Additionally, if an appropriate package type term is not included, the remaining contents of the vial could be "saved" for future use resulting in use of deteriorated drug product medication errors.	We recommend the removal of the text "50 mL." For example, "....in a single-dose vial."
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Revise to: BRANDNAME is supplied as a white to almost white lyophilized powder in single dose vials containing 280 mg landiolol HCl. Each vial is supplied in a carton NDC xxxxx-xx-xx
2.	As currently presented, (b) (4) is included. Additionally, as currently presented, a package	Inclusion of the (b) (4) (b) (4) may be misinterpreted (b) (4)	To minimize the potential for misinterpretation, remove the text (b) (4) Additionally, we recommend adding the package type term,

Table 2. Identified Issues and Recommendations for Division of Cardiology and Nephrology (DCN)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	type term, (i.e., "single-dose") is not included prior to the first occurrence of the word "vial."	Additionally, if an appropriate package type term is not included, the remaining contents of the vial could be "saved" for future use resulting in use of deteriorated drug product medication errors.	"single-dose" prior to the occurrence of the word "vial." For example, BRANDNAME (landiolol) 280 mg for injection (equivalent to 300 mg landiolol HCl) is supplied as a white to almost white lyophilized powder in a single-dose vial."
3.	As currently presented, the (b) (4) (b) (4) (b) (4) and associated text are included in Section 16.	(b) (4) rather than the *How Supplied/Storage and Handling* section of the FPI.	Delete the (b) (4) (b) (4) and associated text currently included in Section 16.

5 RECOMMENDATIONS FOR AOP ORPHAN PHARMACEUTICALS GMBH

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, a graphic design appears (b) (4) proprietary name which is presented in (b) (4) . Placement of the graphic and use of (b) (4) for the proprietary name can lead to misinterpretation.	The proprietary and established names should be the most prominent information on the container label. For more information see the draft guidance for industry, "*Safety Considerations for Container Labels and Carton Labeling Design to*	To prevent misinterpretation of the proprietary name, we recommend decreasing the prominence of the graphic away from the proprietary name. In addition, replace the proprietary name " (b) (4) with "BRANDNAME" or "TRADENAME" until a conditionally acceptable proprietary name is identified

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		Minimize Medication Errors".[d] Furthermore, "The use of logos, stripes, watermark graphics, lines, and symbols on container labels and/or carton labeling may help to differentiate products, but it should not distract the reader from critical information or add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort critical information." "We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name because the logo can look like an additional letter in the proprietary name."[e]	as (b) (4) was denied on October 06, 2033.
2.	As currently presented, the proposed container label and carton labeling denotes a location for the lot number and expiration date.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day.

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

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

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	However, the format for expiration date is not defined.		FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
3.	As currently presented, the product strength is "280 mg" which could lead to confusion.	For dry solid injectable products requiring reconstitution the strength should be expressed in terms of the quantity of drug per vial (e.g., XX mg/vial or XX mg per vial).[f]	To minimize confusion, revise all occurrences of the current strength expression "280 mg" to instead "280 mg/vial" or "280 mg per vial."
4.	As currently presented, your currently proposed name presentation on the principal display panel (PDP) is: (b) (4)	Per 21 CFR 201.10 (g)(1): *"…the established name shall be placed in direct conjunction with the proprietary name or designation, and the*	Revise the name and strength presentations by relocating the dosage form, strength statement, and add brackets (i.e., parentheses) surrounding

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

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	landiolol (b) (4) for injection We note that as currently presented the established name "landiolol" is not enclosed in parentheses.	*relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means."*[g]	the established name as follows: (b) (4) (landiolol) for Injection 280 mg/vial
5.	As currently presented, the established name on the PDP lacks prominence commensurate with the proprietary name and is not at least half the size of the proprietary name.	Per 21 CFR 201.10 (g)(2): *"The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name…"*[h]	Revise the established name to be in accordance with 21 CFR 201.10 (g)(2).
6.	As currently presented, the National Drug Code (NDC) placeholder is included (b) (4) of your proposed container label (vial) and carton labeling.	We are concerned that your current proposed location of the NDC (b) (4) may be missed, as typically the NDC is located at the top of the principal display panel (PDP). Additionally, the NDC number is often used as an additional verification prior to drug dispensing in the retail setting or prior to preparation and/or administration in an inpatient setting and	To provide prominence we recommend that you relocate your proposed NDC placeholder to the top of the PDP.

[g] 21 CFR 201.10(g)(1).

[h] 21 CFR 201.10(g)(2).

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		therefore is an important safety feature.	
7.	As currently presented, the route of administration (b) (4) is included on the PDP of the container label and carton labeling.	The route of administration statement is considered to be "critical information." For more information see the draft guidance for industry, "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*"[i] To avoid medication errors involving wrong route of administration, the route of administration statement should be prominently displayed on the PDP.	Revise the route of administration statement from (b) (4) to instead (b) (4) and increase the prominence on the PDP of the container label and carton labeling.
8.	As currently presented, the package type term (i.e., Single-Dose Vial), does not include the statement "Discard Unused Portion."	The entire contents of the vial could be given as a single dose or the remaining contents "saved" for future use resulting in use of deteriorated drug product medication errors.	To minimize risk of the entire contents of the vial being given as a single dose or remaining contents "saved" for future use, consider revising the statement "Single-Dose Vial" to read "Single-Dose Vial. Discard Unused Portion."
9.	As currently presented, the "Rx only" statement is included within the (b) (4)	Traditionally the "Rx only" statement is positioned on the PDP to ensure its prominence.	Consider relocating the "Rx only" statement to the PDP of the container label and carton labeling, such that it does not compete in size or prominence

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

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) of the container label and carton labeling.		with critical information on the PDP.
10.	As currently presented, the terminology within the recommended dosage statement (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion.	To ensure consistency with the Prescribing Information, we recommend revising the statement, (b) (4) " to read "Recommended Dosage: See prescribing information."
11.	As currently presented, directions for reconstitution included on the container label and carton labeling does not align with the proposed prescribing information (PI) (b) (4)	Inconsistencies in preparation directions (i.e., (b) (4) vs. (b) (4) could result in wrong technique and/or preparation medication errors, wrong concentration medication errors, and wrong dose medication errors.	To prevent wrong technique and/or preparation medication errors, wrong concentration medication errors, and wrong dose medication errors, we recommend that the directions for reconstitution included on the container label and carton labeling be appropriately aligned with the proposed PI (b) (4)
Container Label			
1.	As currently presented, there is no linear barcode included on the container label.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part	Add the product's linear barcode to each individual container label as required per 21CFR 201.25(c)(2). We recommend that the container label linear barcode be oriented in a vertical position to improve scannability of the

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		of the label whenever possible.	barcode, as barcodes placed in a horizontal position may not scan due to the curvature of the container. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
2.	As currently presented, the manufacturer information (b) (4) and takes the readers' attention away from important product information (b) (4)		We recommend you decrease the prominence, font size (height) of the letters within your manufacturer information or consider moving the manufacturer information to the side panel.
Carton Labeling			
1.	As currently presented, there is no linear barcode included on your proposed carton labeling.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the linear barcode to your proposed carton labeling. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
2.	As currently presented, the net quantity statement is missing from your proposed carton labeling.	The net quantity statement should appear on the principal display panel (PDP), but should be separated from and less prominent than the statement of strength (e.g.,	Add the net quantity statement (i.e., "One vial") to the PDP of your proposed carton labeling. For additional information, see 21 CFR 201.51.

Table 3. Identified Issues and Recommendations for AOP Orphan Pharmaceuticals GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		not highlighted, boxed, or bolded).[j]	

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for landiolol that AOP Orphan Pharmaceuticals GmbH submitted on January 3, 2023.

Table 4. Relevant Product Information for landiolol hydrochloride	
Initial Approval Date	N/A
Active Ingredient	landiolol
Indication	For the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	280 mg/vial
Dose and Frequency	**Dosing for Patients with Normal Cardiac Function**: administered as a continuous intravenous (IV) infusion with or without a bolus loading dose. Table 1: (b) (4) Dosing (b) (4) (b) (4) . **Dosing for Patients with Impaired Cardiac Function or** (b) (4) administered as a continuous intravenous infusion. (b) (4) Dosing (b) (4) (b) (4) . **Transition from landiolol Injection therapy to Alternate Drugs:** After achieving adequate control of the heart rate and a stable clinical status, transition to alternative medicinal products (such as oral antiarrhythmics) may be accomplished.

	When landiolol is replaced by alternative drugs, the physician should carefully consider the labeling and dosage of the alternative drug. If switched to an oral beta-blocker the dosage of landiolol can be reduced as follows: • Ten minutes after administration of the alternative, the infusion rate of landiolol can be reduced by one-half (50%). • The patient's response should be supervised, and if satisfactory control is maintained for at least one hour, the landiolol infusion can be discontinued.
How Supplied	landiolol 280 mg for injection (equivalent to 300 mg landiolol HCl) in 50 mL vial. Carton containing one (1) single-dose vial.
Storage	Store unreconstituted product at 20°C to 25°C (68ºF to 77ºF) [see USP Controlled Room Temperature], with excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Each vial contains no preservative. Once the vial content has been reconstituted, (b) (4) with any unused portion discarded.
Container Closure	The vials are closed with a (b) (4) rubber stopper and sealed with an aluminum flip-off (yellow) cap. Secondary packaging consists of a carton box.

APPENDIX E. OTHER

FDA Information Request dated December 13, 2022[k]: We note that the Prescribing Information (PI) states (b) (4)

(b) (4)

Applicant response received on 12/19/22. See: \\CDSESUB1\EVSPROD\nda217202\0021\m1\us\111-information-amendment\response-to-fda-request-for-information-clinical-and-labelli.pdf.

[k] Changi, M. FDA Communication: New Information request NDA 217202. Silver Spring (MD): FDA, CDER, OND, DCN (US); 2022 DEC 13. NDA 217202. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806a204e.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following landiolol labels and labeling submitted by AOP Orphan Pharmaceuticals GmbH.

- Container label received on January 3, 2023
- Carton labeling received on January 3, 3023
- Prescribing Information (PI) (Image not shown) received on January 3, 2023:
    - Cleaned proposed (Draft) PI available from the following link: \\CDSESUB1\EVSPROD\nda217202\0020\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx.
    - Annotated version PI available at the following link: \\CDSESUB1\EVSPROD\nda217202\0020\m1\us\114-labeling\draft\labeling\draft-labelling-text_track.pdf.

F.2 Label and Labeling Images

Container label

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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