CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216834Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION: Approval

NDA 216834
Addendum to Review # 1

This addendum to the Integrated Quality Assessment (IQA) for NDA 216834 dated 6/6/2023 conveys the final Office of Pharmaceutical Quality (OPQ) recommendation for the application. Labeling deficiencies identified during the initial review have been adequately addressed and the OPQ review team recommends that the NDA be approved.

NDA Executive Summary

1. Application/Product Information

NDA Number	216834		
Applicant Name	UCB Inc.		
Drug Product Name	Zilucoplan		
Dosage Form	Injection		
Proposed Strength(s)	16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.81 mL		
Route of Administration	Subcutaneous		
Maximum Daily Dose	32.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.		
Drug Product Description	Clear to slightly opalescent, colorless solution in a single-dose prefilled syringe.		
Co-packaged product information	N/A		
Device information	1 mL [redacted] (b) (4) glass syringe with staked 29G, ½" thin wall needle, rigid needle shield, and [redacted] (b) (4) rubber plunger/stopper assembled with needle safety device		
Storage Temperature/ Conditions	2°C to 8°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Venkateswara Pavuluri	Martha Heimann
	Manufacturing	Khalid Khan	Cassandra Abellard
	Biopharmaceutics	N/A	N/A

	Microbiology	Helen Ngai	Paul Dexter
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	Device aspects of the product (syringe and needle shield) were reviewed by Papatya Kaner (CDRH/OPEQ). Her review, dated 5/8/2023, recommends approval of the application.		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

36 months for product stored refrigerated (2°C to 8°C).

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The OPQ review team recommends Approval of NDA 216834 for ZILBRYSQ (zilucoplan injection). The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

The initial OPQ integrated review for NDA 216834, dated June 6, 2023, was "Pending" due to extensive labeling deficiencies. The labeling deficiencies were resolved during labeling negotiations with applicant. Thus, there are no outstanding deficiencies that would preclude approval of the application.

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 - N/A
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:

There are no outstanding quality concerns or lifecycle considerations.

Martha Heimann

Digitally signed by Martha Heimann
Date: 8/23/2023 03:05:54PM
GUID: 504f845f00000ed260627d268a8cdc9d

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **21-AUG-2023**

From: **Venkateswara R. Pavuluri, PhD, R. Ph.**
Drug Product Reviewer, DNDPII
Office of New Drug Products

Through: **Martha R. Heimann, PhD.**
SPQA, Br3/ DNDPII
Office of New Drug Products

To: **CMC Labeling Review for Zilucoplan Injection (NDA 216834)**
Subject: Final Recommendation APPROVAL

At the time when initial Labeling Review of NDA 216834 was completed on 30-MAY-2023, this NDA was not recommended for approval 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective due to deficiencies for PI, Med. Guide, IFU and Carton and container labels as listed below. The NDA for this drug product was otherwise complete and adequate from the drug product perspective, per the review dated 30-MAY-2023. This labeling memo is based on the Amendments (eCTD SN 0047, dated 25-JUL-2023 and SN 0050, dated 11-AUG-2023; and updated PI received via email on 14-JAUG-2023).

Labeling/Label Deficiencies identified in CMC Labeling review as of 30-MAY-2023:

A. Prescribing Information and Medication Guide:

1. *Revise the 'Dosage Forms and Strengths' section of 'Highlights' to indicate that the dose is based on zilucoplan free acid, e.g., Injection: 16.6 mg /0.416 mL, 23.0 mg /0.574 mL, and 32.4 mg /0.810 mL zilucoplan in single-dose prefilled syringes.*

   Applicant's Response (email dated 14-AU-2023): Applicant revised the statement as suggested by FDA.

Reviewer's Evaluation: Adequate.

2. *Revise 'Dosage Forms and Strengths' section of PI to indicate that the dose is based on zilucoplan free acid, e.g.,* (b) (4) *16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL in single-dose prefilled syringes.*

Applicant's Response (email dated 14-AUG-2023): Statement revised as "Injection: 16.6 mg/0.416 mL, 23 mg/0.574 mL, or 32.4 mg/0.81 mL of zilucoplan as a clear to slightly opalescent, colorless solution in single-dose prefilled syringes."

Reviewer's Evaluation: Adequate.

3. *Revise the first sentence in second paragraph of 'Description' section of PI to read as: ZILBRYSQ injection is a sterile, clear to slightly opalescent, colorless, preservative-free, buffered solution of zilucoplan (as zilucoplan sodium) for subcutaneous injection, in single-dose prefilled syringe. The solution pH is between 6.5 and 7.5.*

   Applicant's Response (eCTD SN 0014 dated 31-JAN-2023): Applicant revised the statements as proposed by FDA.

Reviewer's Evaluation: Adequate.

4. *For products that contain an active ingredient that is a salt, an equivalency statement shall be included under 'Description', section of PI reflecting the names and strengths of both the active ingredient (salt) and the active moiety (free acid), per Guidance for industry: Naming of Drug Products Containing Salt Drug Substances (June 2015) and MAPP 5021.1 the Naming of Drug Products Containing Salt Drug Substances (December 2017).*

   Include the following statement in 'Description' section of the PI: ZILBRYSQ is supplied in three dose strengths containing 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL of zilucoplan free acid equivalent to 17.0 (b) (4) mg, 23 (b) (4) mg, and 33.20 mg of zilucoplan sodium respectively.

   Applicant's Response (email dated 14-AUG-2023): Applicant proposes to add "ZILBRYSQ is supplied in three dose strengths containing 16.6 mg /0.416 mL, 23 mg /0.574 mL, and 32.4 mg/0.81 mL of zilucoplan free acid equivalent to 17.0 mg, 23.6 mg, and 33.2 mg of zilucoplan sodium, respectively.", omitting the second decimal point in theoretical equivalent value of 17.0 (b) (4) mg zilucoplan sodium.

Reviewer's Evaluation: Acceptable. Agency recommends leaving out the "0" after decimal point and state as '17 mg' instead of '17.0 mg' to prevent medication errors.

5. *List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable. Revise the second sentence in second paragraph of 'Description' section of PI, to read as: Additionally, each mL of the solution contains dibasic sodium phosphate, anhydrous (4.11 mg); monobasic sodium phosphate, monohydrate (2.9 mg); sodium chloride (4.42 mg) and Water for Injection, (b) (4)*

Applicant's Response (email dated 14-AUG-2023): Applicant proposes to add "Additionally, each mL of the solution contains dibasic sodium phosphate, anhydrous (4.11 mg); monobasic sodium phosphate, monohydrate (2.9 mg); sodium chloride (4.42 mg); and water for injection."

Reviewer's Evaluation: Adequate.

6. *Include chemical name and structural formula for the drug (zilucoplan sodium), required per 21 CFR 201.57(c)(12)(1)(F).*

   Applicant's Response (email dated 14-AUG-2023): Applicant included the chemical name and primary structure for zilucoplan sodium.

Reviewer's Evaluation: Adequate.

7. *Revise the storage conditions in the text and tables under section 16.2 Storage and Handling of PI with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis, e.g., Store ZILBRYSQ prefilled syringes refrigerated at 2° to 8°C (36° to 46°F) in the original carton until dispensing. Do not freeze.*

   Applicant's Response (email dated 14-AUG-2023): Applicant revised the storage statement as proposed by FDA.

Reviewer's Evaluation: Adequate.

8. *Revise the storage conditions in the text and tables in Medication Guide with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis.*

   Applicant's Response: Applicant is expected to align the storage statements in Medication Guide in line with storage conditions in PI and will be verified when submitted.

Reviewer's Evaluation: Acceptable.

9. *List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable.*

   Applicant's Response: Applicant is expected to align the list the inactive ingredients in Medication Guide in line with PI and will be verified when submitted.

Reviewer's Evaluation: Acceptable

Container Labels:

10. *Provide the format of lot number to be used for commercial batches. The assigned lot number shall comply with the requirements of 21 CFR*

201.100(b)(6), i.e., provide the complete manufacturing history of the package of the drug.

Applicant's Response: Applicant proposes to add a placeholder for the 2D matrix on both the inner and outer cartons which include the following information: NDC, expiration date and lot number. The outer carton is the smallest individual saleable unit.

Reviewer's Evaluation: Acceptable

11. *Identify the expiration date format you intend to use. 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.*

    Applicant's Response (eCTD SN 0047, dated 25-JUL-2023): Applicant proposed the format of the expiration date on the carton labeling as YYYY-MMM-DD where alphabetical characters will be used to represent the month.

Reviewer's Evaluation: Adequate.

12. *List names of all inactive ingredients in alphabetical order, using current USP/NF names where applicable. Also delete the statement* (b) (4) *from all carton labels.*

    Applicant's Response (eCTD SN 0047, dated 25-JUL-2023 and eCTD SN 0050, dated 11-AUG-2023): Applicant listed all inactive ingredients in alphabetical order, using current USP/NF names where applicable and deleted the statement (b) (4) from all proposed carton labels to be launched upon approval. Applicant stated that (b) (4) 4 inner carton containing 7-units with a total of 28 of prefilled syringes each are packaged in to the outer commercial pack.

Reviewer's Evaluation: Adequate.

13. *All container and carton labels must bear the barcodes that meet requirements specified under 21 CFR 201.25(c), unless specifically exempt from such requirement as stated under 21 CFR 201.25(d). Therefore, include a bar code on all carton and container labels that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code.*

    Applicant Response (eCTD SN 0047, dated 25-JUL-2023 and eCTD SN 0050, dated 11-AUG-2023): In the 25-JUL-2023 response that addition of the linear barcode in the container labels would preclude availability of unobstructed areas of the syringe for visual inspection of the product, as required per the 'Instructions for

Use'. However, up on a follow up request for information advising them that Bar code is a requirement, Applicant provided sample labels for prefilled syringes with the linear bar code, (b) (4)

Reviewer's Evaluation: **Adequate**.

The following comments were sent to Applicant that are applicable to all carton and container labels submitted in eCTD SN 0047, 7/25/23.

1. *Under the inactive ingredients list the wording "Water for Injection* (b) (4) *has to be replaced with "water for injection"*
2. *The units of measure for storage temperature shall be revised as "2°C to 8°C (36°F to 46°F)" stating in degree Celsius (°C), followed by degrees Fahrenheit (°F) in parenthesis.*

Applicant Response (eCTD SN 0050, dated 11-AUG-2023): Applicant updated the information on carton and container labels as suggested.

Reviewer's Evaluation: **Adequate**.

Following additional comments sent to Applicant for revising the PI, and carton labels as of Aug 21, 2023. The revised labeling information submitted by Applicant will be verified for necessary minor corrections up on receipt.

1. *On all carton labels, revise the statement* (b) (4) *to be read as" Each single-dose prefilled syringe contains: XX mg zilucoplan (equivalent to zilucoplan sodium YY mg); dibasic sodium phosphate, anhydrous; monobasic sodium phosphate, monohydrate; sodium chloride; and water for injection.*

2. *We refer to your proposal under section 11 of the PI (PI received via email on Aug 14, 2023) to use "17.0 mg, for the amount of zilucoplan sodium' in the equivalency statement. While your proposal for removal of the decimal point in the zilucoplan sodium content (17.0 mg in place of the theoretical amount of 17.0* (b) (4) *mg) is acceptable, we recommend whole number "17 mg" leaving out the "0" after decimal point. This change shall be made in section 11 of the PI, and the carton and container labels for 16.6 mg strength.*

Recommendation:

The CMC label/labeling issues identified in the labeling review have been satisfactorily resolved, as reproduced in attachment below. This application is recommended for APPROVAL from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, PhD, R. Ph.,
Drug Product Reviewer
DNDP II, ONDP

Martha Heimann, PhD,
SPQA, Branch 3, DNDP II, ONDP

Annexure - 1

HDPE Bottle and shell pack label samples as submitted eCTD SN 0014 on 31-JAN-2023

Tracked Changes:

Cleaner Version:

Tracked Changes:

Cleaner Version:

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 8/21/2023 02:39:29PM
GUID: 551eb409003b6d46b8d5dfa7699e4742

Martha Heimann

Digitally signed by Martha Heimann
Date: 8/21/2023 04:41:53PM
GUID: 504f845f00000ed260627d268a8cdc9d

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

/s/

MARTHA R HEIMANN
08/23/2023 03:36:55 PM

NDA Executive Summary

1. Application/Product Information

NDA Number	216834		
Applicant Name	UCB Inc.		
Drug Product Name	Zilucoplan		
Dosage Form	Injection		
Proposed Strength(s)	16.6 mg/0.416 mL, 23 mg/0.574 mL, 32.4 mg/0.810 mL		
Route of Administration	Subcutaneous		
Maximum Daily Dose	32.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.		
Drug Product Description	Clear to slightly opalescent, colorless solution in a single-dose prefilled syringe.		
Co-packaged product information	N/A		
Device information	1 mL (b) (4) glass syringe with staked 29G, ½" thin wall needle, rigid needle shield, and (b) (4) rubber plunger/stopper assembled with needle safety device		
Storage Temperature/ Conditions	2°C to 8°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Venkateswara Pavuluri	Martha Heimann
	Manufacturing	Khalid Khan	Cassandra Abellard

	Biopharmaceutics	N/A	N/A
	Microbiology	Helen Ngai	Paul Dexter
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	Device aspects of the product (syringe and needle shield) were reviewed by Papatya Kaner (CDRH/OPEQ). Her review, dated 5/8/2023, recommends approval of the application.		

2. Final Overall Recommendation - Pending

3. Comments:

Labeling deficiencies are listed on page 4.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The OPQ recommendation is pending for NDA 216834 for ZILBRYSQ (zilucoplan injection). The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. However, the proposed labeling and labels are inadequate to meet the regulatory requirements. The labeling deficiencies may be resolved during labeling negotiations if no other disciplines identify deficiencies that would preclude approval. The OPQ recommendation will be updated prior to final action.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Inadequate
Manufacturing - Adequate
Biopharmaceutics - N/A
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:

Except for labeling, there are no outstanding quality concerns or lifecycle considerations.

List of Deficiencies:

A. Highlights of Prescribing Information

i. Revise the 'Dosage Forms and Strengths' section of 'Highlights' to indicate that the dose is based on zilucoplan free acid, e.g., Injection: 16.6 mg /0.416 mL, 23.0 mg /0.574 mL, and 32.4 mg /0.810 mL zilucoplan in single-dose prefilled syringes.

B. Full Prescribing Information:

1. DOSAGE FORMS AND STRENGTHS

ii. Revise 'Dosage Forms and Strengths' section of PI to indicate that the dose is based on zilucoplan free acid, e.g., (b) (4) 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL in single-dose prefilled syringes.

2. DESCRIPTION

iii. Revise the first sentence in second paragraph of 'Description' section of PI to read as: ZILBRYSQ injection is a sterile, clear to slightly opalescent, colorless, preservative-free, buffered solution of zilucoplan (as zilucoplan sodium) for subcutaneous injection, in single-dose prefilled syringe. The solution pH is between 6.5 and 7.5.

iv. For products that contain an active ingredient that is a salt, an equivalency statement shall be included under 'Description', section of PI reflecting the names and strengths of both the active ingredient (salt) and the active moiety (free acid), per Guidance for industry: Naming of Drug Products Containing Salt Drug Substances (June 2015) and MAPP 5021.1 the Naming of Drug Products Containing Salt Drug Substances (December 2017).

Include the following statement in 'Description' section of the PI: ZILBRYSQ is supplied in three dose strengths containing 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL of zilucoplan free acid equivalent to 17.0 (b) (4) mg, 23. (b) (4) mg, and 33.20 mg of zilucoplan sodium respectively.

v. List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable. Revise the second sentence in second paragraph of 'Description' section of PI, to read as: Additionally, each mL of the solution contains dibasic sodium phosphate, anhydrous (4.11 mg);

monobasic sodium phosphate, monohydrate (2.9 mg); sodium chloride (4.42 mg) and Water for Injection (b) (4)

vi. *Include chemical name and structural formula for the drug (zilucoplan sodium), required per 21 CFR 201.57(c)(12)(1)(F).*

3. HOW SUPPLIED/STORAGE AND HANDLING

vii. Revise the storage conditions in the text and tables under section 16.2 Storage and Handling of PI with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis, e.g., Store ZILBRYSQ prefilled syringes refrigerated at 2° to 8°C (36° to 46°F) in the original carton until dispensing. Do not freeze.

C. Medication Guide and IFU:

viii. Revise the storage conditions in the text and tables in Medication Guide with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis,

ix. List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable.

D. Container Labels:

x. Provide the format of lot number to be used for commercial batches. The assigned lot number shall comply with the requirements of 21 FR 201.100(b)(6), i.e., provide the complete manufacturing history of the package of the drug.

xi. Identify the expiration date format you intend to use. 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.

xii. List names of all inactive ingredients in alphabetical order, using current USP/NF names where applicable. Also remove the statement (b) (4) (b) (4) *from all carton labels.*

xiii. All container and carton labels must bear the barcodes that meet requirements specified under 21 CFR 201.25(c), unless specifically exempt from such requirement as stated under 21 CFR 201.25(d). Therefore, include a bar code on all carton and container labels that contains, at a minimum, the National Drug Code (NDC) number in a linear bar code.

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

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: eCTD SN 001; dated 31-AUG-2022

(b) (4)

[redacted]

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
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.	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Dose expression is based on Free acid form. *Comment to Applicant: Revise the 'Dosage Forms and Strengths' section of 'Highlights' to indicate that the dose is based on zilucoplan free acid, e.g.,* Injection: 16.6 mg /0.416 mL, 23.0 mg /0.574 mL, and 32.4 mg /0.810 mL zilucoplan in single-dose prefilled syringes.

1.2 FULL PRESCRIBING INFORMATION

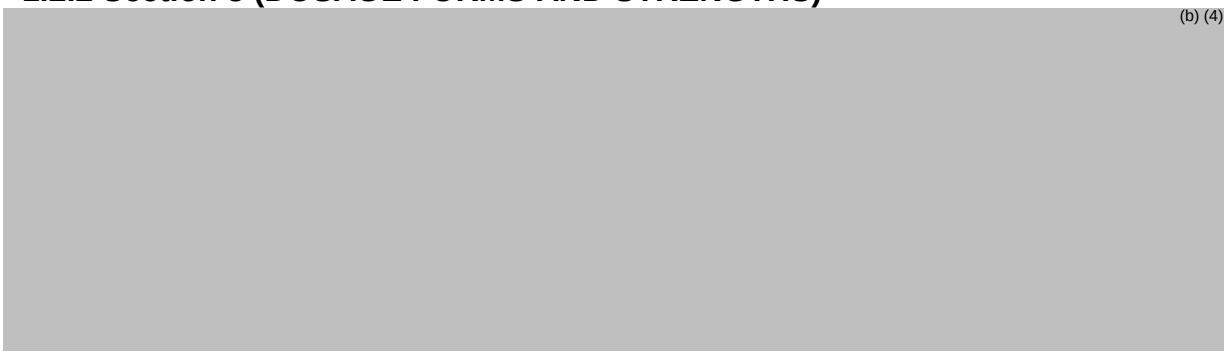
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed	N/A	

to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Inadequate	Dose is based on zilucoplan free acid form. *Revise 'Dosage Forms and Strengths' section of PI to indicate that the dose is based on zilucoplan free acid, e.g.,* (b) (4) 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL in single-dose prefilled syringes.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Inadequate	*Comment to Applicant: Revise the first sentence in second paragraph of 'Description' section of PI to read as: ZILBRYSQ injection is a sterile, clear to slightly opalescent, colorless, preservative-free, buffered solution of zilucoplan (as zilucoplan sodium) for subcutaneous injection, in single-dose prefilled syringe. The solution pH is between 6.5 and 7.5.*
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Inadequate	Dose is based on free acid form. *Comment to Applicant: For products that contain an active ingredient that is a salt, an equivalency statement shall be included under 'Description', section of PI reflecting the names and strengths of both the active ingredient (salt) and the active moiety, per Guidance for industry: Naming of Drug Products Containing Salt Drug Substances (June 2015) and MAPP 5021.1 the Naming of Drug Products Containing Salt Drug Substances (December 2017).* *Include the following statement in 'Description' section of the PI: ZILBRYSQ is supplied in three dose strengths containing 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL of zilucoplan free acid equivalent to 17.0 (b)(4) mg, 23. (b)(4) mg and 33.20 mg of zilucoplan sodium respectively.*

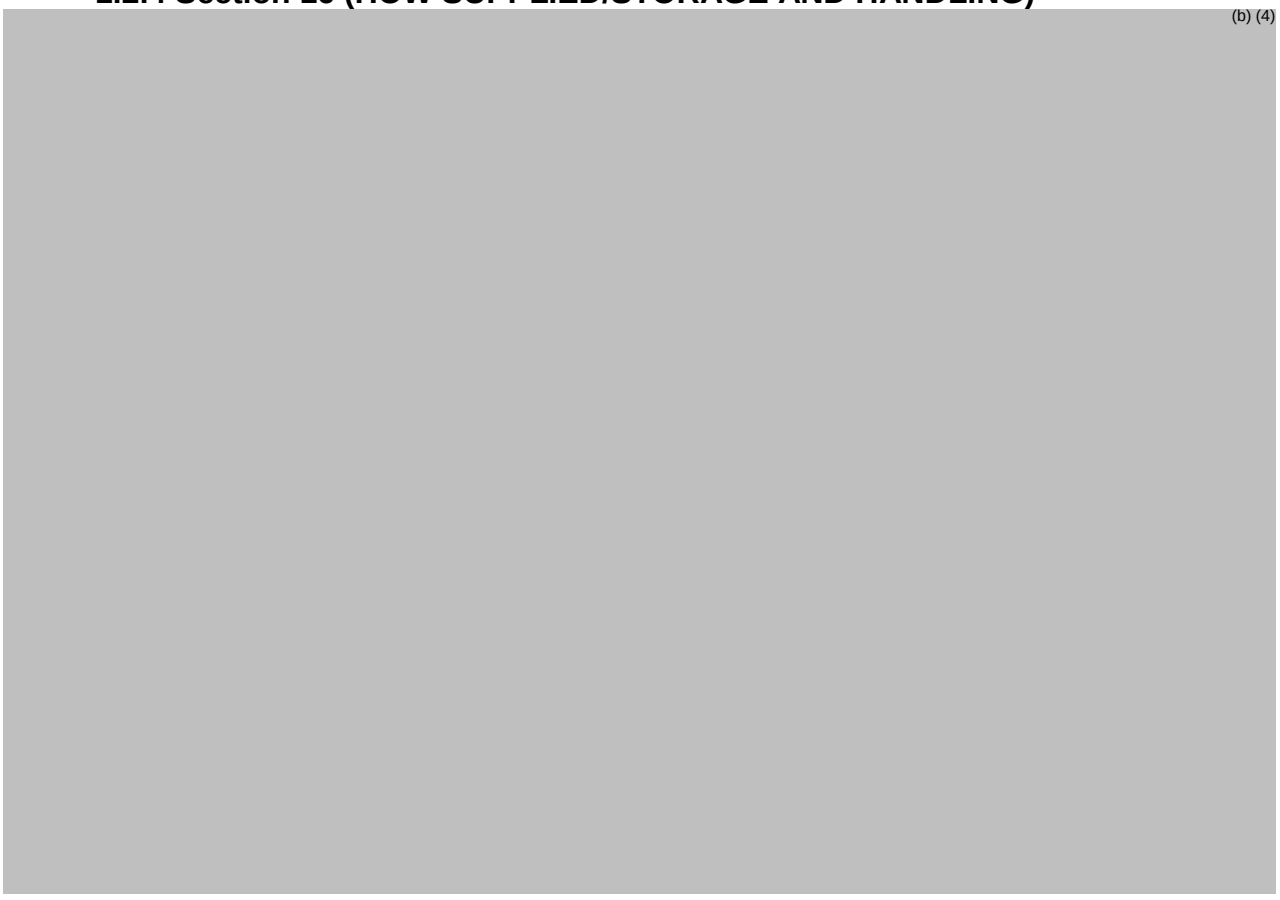
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	*Comment to Applicant:* *List the names of all inactive ingredients in alphabetical order, using USP/NF names where applicable.* *Revise the second sentence in second paragraph of 'Description' section of PI, to read as: Additionally, each mL of the solution contains dibasic sodium phosphate, anhydrous (4.11 mg); monobasic sodium phosphate, monohydrate (2.9 mg); sodium chloride (4.42 mg) and Water for Injection,* (b) (4)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Inadequate	*Comment to Applicant: Include chemical name and structural formula for the drug (zilucoplan sodium), required per 21 CFR 201.57(c)(12)(1)(F)*
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	ZILBRYSQ (zilucoplan) injection prefilled syringe
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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.	Adequate	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^{x}" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	*Comment to the Applicant: Revise the storage conditions in the text and tables under section 16.2 Storage and Handling of PI with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis, e.g., Store ZILBRYSQ prefilled syringes refrigerated at 2° to 8°C (36° to 46°F) in the original carton until dispensing. Do not freeze.*
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	prefilled syringe components are not made with natural rubber latex.
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured for: UCB, Inc. 1950 Lake Park Drive Smyrna, GA 30080

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	Applicable to MG and IFU
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	MG and IFU
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	For both MG and PI, *Comment to Applicant: List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable.*
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Refer to "ITEMS FOR ADDITIONAL ASSESSMENT." For deficiencies identified in PI, IFU and Medication Guide,

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)

3.2 Carton Labeling

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Deferred to DMEPA Decision about prominence (type and font size) of the established name in relation to the Brand/trade name.
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Dose is based on free acid form
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Inadequate	*Comments to Applicant:* 1. *Provide the format of lot number to be used for commercial batches. The assigned lot number shall comply with the requirements of 21 FR 201.100(b)(6),i.e., provide the complete manufacturing history of the package of the drug.* 2. *Identify the expiration date format you intend to use. 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.*
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

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, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	*Comment to Applicant: List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable. Also delete the statement* (b) (4) *from all carton labels.*
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Bar code is present on outer cartons for 7 units pack only. *Comment to Applicant: All container and carton labels must bear the barcodes that meet requirements specified under 21 CFR 201.25(c), unless specifically exempt from such requirement as stated under 21 CFR 201.25(d). Therefore, include a bar code on all carton and container labels that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code.*

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Inadequate.

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies:

A. Highlights of Prescribing Information

i. Revise the 'Dosage Forms and Strengths' section of 'Highlights' to indicate that the dose is based on zilucoplan free acid, e.g., Injection: 16.6 mg /0.416 mL, 23.0 mg /0.574 mL, and 32.4 mg /0.810 mL zilucoplan in single-dose prefilled syringes.

B. Full Prescribing Information:

1. DOSAGE FORMS AND STRENGTHS

ii. *Revise 'Dosage Forms and Strengths' section of PI to indicate that the dose is based on zilucoplan free acid, e.g., (b) (4) 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL in single-dose prefilled syringes.*

2. DECRIPTION

iii. *Revise the first sentence in second paragraph of 'Description' section of PI to read as: ZILBRYSQ injection is a sterile, clear to slightly opalescent, colorless, preservative-free, buffered solution of zilucoplan (as zilucoplan sodium) for subcutaneous injection, in single-dose prefilled syringe. The solution pH is between 6.5 and 7.5.*

iv. *For products that contain an active ingredient that is a salt, an equivalency statement shall be included under 'Description', section of PI reflecting the names and strengths of both the active ingredient (salt) and the active moiety (free acid), per Guidance for industry: Naming of Drug Products Containing Salt Drug Substances (June 2015) and MAPP 5021.1 the Naming of Drug Products Containing Salt Drug Substances (December 2017).*

Include the following statement in 'Description' section of the PI: ZILBRYSQ is supplied in three dose strengths containing 16.6 mg /0.416 mL, 23.0 mg /0.574 mL and 32.4 mg /0.810 mL of zilucoplan free acid equivalent to 17.0 (b) (4) mg, 23 (b) (4) mg and 33.20 mg of zilucoplan sodium respectively.

v. *List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable. Revise the second sentence in second paragraph of 'Description' section of PI, to read as: Additionally, each mL of the solution contains dibasic sodium phosphate, anhydrous (4.11 mg); monobasic sodium phosphate, monohydrate (2.9 mg); sodium chloride (4.42 mg) and Water for Injection, (b) (4)*

vi. *Include chemical name and structural formula for the drug (zilucoplan sodium), required per 21 CFR 201.57(c)(12)(1)(F).*

3. HOW SUPPLIED/STORAGE AND HANDLING

vii. *Revise the storage conditions in the text and tables under section 16.2 Storage and Handling of PI with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis, e.g., Store ZILBRYSQ prefilled syringes refrigerated at 2° to 8°C (36° to 46°F) in the original carton until dispensing. Do not freeze.*

C. Medication Guide and IFU:

viii. Revise the storage conditions in the text and tables in Medication Guide with temperatures expressed in SI units, i.e., Celsius (°C) followed by equivalent Fahrenheit (°F) units in parenthesis,

ix. List names of all inactive ingredients in alphabetical order, using USP/NF names where applicable.

D. Container Labels:

x. Provide the format of lot number to be used for commercial batches. The assigned lot number shall comply with the requirements of 21 FR 201.100(b)(6), i.e., provide the complete manufacturing history of the package of the drug.

xi. Identify the expiration date format you intend to use. 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.

xii. List names of all inactive ingredients in alphabetical order, using current USP/NF names where applicable. Also delete the statement (b) (4) *from all carton labels.*

xiii. All container and carton labels must bear the barcodes that meet requirements specified under 21 CFR 201.25(c), unless specifically exempt from such requirement as stated under 21 CFR 201.25(d). Therefore, include a bar code on all carton and container labels that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code.

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective until the remaining deficiencies delineated in the List of Deficiencies (for PI, Med. Guide, IFU and Carton and container labels) above are satisfactorily resolved. The above deficiencies will be resolved by sending request for information and through labeling negotiation with Applicant prior to final approval.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, PhD, R. Ph.; 27-MAY-2023

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

Martha Heimann, PhD, __ -MAY-2023

Venkateswara Pavuluri

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Martha Heimann

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CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	216834
Assessment Cycle Number	1
Drug Product Name / Strength	Established name: Zilucoplan. Proprietary name: ZILBRYSQ. Strength: 40 mg/mL.
Route of Administration	Subcutaneous injection
Applicant Name	Ra Pharmaceuticals now part of UCB, Inc.*
Therapeutic Classification/ OND Division	CDER/OND/ON/DN1
Manufacturing Site	(b) (4)
Method of Sterilization	

* The applicant name on the 356H form is, 'Ra Pharmaceuticals now part of UCB, Inc.' The cover letter indicates the sponsor is UCB, Inc, where all questions and correspondences are directed.

Assessment Recommendation: **Adequate**

Assessment Summary: The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig -1 (SD # 1)	8/31/2022
Orig-1 (SD # 5)	9/28/2022
Orig 1 (SD 10)	1/12/2023
Orig 1 (SD 16)	2/24/2023
Orig 1 (SD 21)	3/8/2023

Highlight Key Issues from Last Cycle and Their Resolution: none

Remarks: The internal goal dates include 74 day letter: 11/13/2022, CMC mid cycle meeting 1/26/2023, OND internal midcycle meeting 2/1/203, mid cycle meeting with applicant 2/16/2023, QDD 4/14/2023 and OND wrap up meeting 7/13/2023.

(b) (4) (b) (4) The review is referenced for the same manufacturing facility CCIT using syringes, dye ingress method and visual examination.

(b) (4) The BLA and review are referenced (b) (4)

Concise Description of Outstanding Issues : none

Supporting Documents:

(b) (4) Relevant information is referenced to: (b) (4)

S DRUG SUBSTANCE

S.2. Manufacture

(b) (4)

Assessment: **Adequate**

S.4 Control of drug substance

(b) (4)

Assessment: **Adequate.** The microbial limits are less than the USP <1111> acceptance criteria for nonsterile substances for pharmaceutical use.

P Drug Product

P.1 Description of the composition of the drug product

- Drug product composition – The drug product is an opalescent, sterile, preservative free solution, formulated at 40 mg/mL concentration, suitable for administration by subcutaneous injection. Zilucoplan drug product is provided in 3 dose presentations with extractable volumes of not less than: 16.6 mg/ 0.416 mL, 23.0 mg/ 0.574 mL and 32.4 mg/ 0.810 mL. The solutions are supplied in 1 mL long (b) (4) glass pre-filled syringes.

3Ingredient	Quantity (mg/mL)	Quantity per dose (mg)			Function
	40 mg/mL	16.6 mg / 0.416 mL	23.0 mg / 0.574 mL	32.4 mg / 0.810 mL	

Zilucoplan (mg)	40.0	16.6 (b) (4)	(b) (4)	32.40	Active ingredient
Monobasic sodium phosphate, monohydrate (mg)	2.90	(b) (4)			
Dibasic sodium phosphate, anhydrous (mg)	4.11				
Sodium chloride (mg)	4.42				
WFI	(b) (4)				

(b) (4)

- Description of container closure system – (b) (4) syringe system with needle and rigid needle shield.

Configuration	Component	Description	Manufacturer
0.416 mL, 0.574 mL and 0.810 mL	Syringe	Glass barrel: 1 mL long (b) (4) glass. Needle: Staked stainless steel, 29G ½" thin wall needle. Needle shield: (b) (4).	(b) (4)
	Stopper	(b) (4) rubber	

Additional Information & Analysis: The syringe is assembled with a safety syringe device referred to as the zilucoplan-SS. The safety syringe device is not in direct contact with the sterile drug product.

Assessment: <u>Adequate</u>. The drug product description, composition, batch size, container closure description are adequately described. It is noted that the commercial batch size (b) (4)

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Helen Ngai

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Paul Dexter

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/s/

MARTHA R HEIMANN
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