CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216483Orig1s000

PRODUCT QUALITY REVIEW(S)

Addendum to OPQ Review (dated March 19, 2024, in DARRTS)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216483
Applicant Name	Utility Therapeutics Ltd
Drug Product Name	PIVYA (pivmecillinam) tablets
Dosage Form.	Tablet
Proposed Strength(s)	185 mg
Route of Administration	Oral
Maximum Daily Dose	555 mg pivmecillinam (one tablet three times daily)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible *E.coli, Proteus mirabilis and Staphylococcus saprophyticus.*
Drug Product Description	The proposed drug product is an immediate release film coated tablet for oral administration. The proposed tablet is a white, circular-shaped, film-coated tablet with a letter "P" (b) (4) on one side and blank on the other, which contains mostly standard compendial excipients in addition to 200 mg of pivmecillinam hydrochloride (200 mg pivmecillinam hydrochloride corresponds to 185 mg pivmecillinam). The proposed commercial container closure system is a single-dose (b) (4) (b) (4) aluminum/ (b) (4) aluminum blister.
Co-packaged product information	N/A
Device information:	N/A
Storage Temperature/ Conditions	20 °C -25 °C

	Discipline	Primary	Secondary
Review Team	*Drug Substance*	Raymond Frankewich	Katherine Windsor
	Drug Product/ Labeling	Jessica Zarenkiewicz	Dorota Matecka
	Manufacturing	Jiao Yang	Nathan Davis
	Biopharmaceutics	Jing Li	Elsbeth Chikhale
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	

2. Final Overall Recommendation **Approval with QPAs**

3. Action Letter Information

a. Expiration Dating:

36 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

b. Additional Comments for Action

The following Post-Marketing Commitment (PMC) should be included in the action letter:

PMC 4603-6

Conduct studies and generate data to finalize the regulatory dissolution specification (method and acceptance criterion) for the drug product (pivmecillinam tablets, 185 mg) to be used at batch release and for stability studies.

The timetable you submitted on March 22, 2024, states that you will conduct this study according to the following schedule:

Interim Report: 10/2024
Final Report: 05/2025

The final report should be submitted to your NDA as a prior approval supplement. The final report submission should be identified as "Final Report Submission for PMC 4603-6" in addition to being identified as a "Prior Approval Supplement".

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substance (pivmecillinam hydrochloride) and the drug product (pivmecillinam tablets). The majority of the CMC information and data for pivmecillinam hydrochloride drug substance were provided via a reference to a Type II DMF (b) (4); the overall drug substance information submitted in the DMF, and the NDA was found adequate (refer to the Drug Substance Review included in the OPQ Review dated March 19, 2024). In response to the FDA question regarding the USAN status of the pivmecillinam hydrochloride name, the Applicant has provided a confirmation that both names, pivmecillinam and pivmecillinam hydrochloride, have been adopted by the USAN Council (refer to the amendments dated February 28 and March 5, 2024). In addition, all comments and requests for additional information, identified during the NDA review by the Drug Product and Manufacturing reviewers have been adequately addressed and resolved (for details refer to the Drug Product and Manufacturing Reviews included in the OPQ Review dated March 19, 2024). The currently proposed commercial blister card is not perforated; therefore, DMEPA has recommended adding a grid line to the blister sheet label to aid cutting while dispensing the correct number of tablets. (b) (4) . From the Biopharmaceutics perspective, limited information was provided regarding the dissolution method development for the proposed commercial drug product. Therefore, the proposed dissolution method and acceptance criteria have been found acceptable on an interim basis with additional dissolution studies to be performed via a PMC study (as indicated above). The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation for this NDA was entered in Panorama by the Office of Pharmaceutical Manufacturing Assessment on February 6, 2024. Several labeling revisions have been recommended in the Product Quality related sections of the Prescribing information (PI) as well as in the container label and carton labeling (e.g., properly displaying the drug product name and strength along with the salt equivalency statement; refer to the Labeling

Review included in the OPQ review dated March 19, 2024). These comments have been conveyed to and accepted by the Applicant. In addition, a 9-count blister was added as another packaging configuration (with no changes to the blister materials or manufacturing process; refer to the updated Labeling Review, below). Therefore, the overall approvability recommendation for this NDA by the Office of Pharmaceutical Quality (OPQ) is Approval with QPAs.

Note: This Addendum (to the OPQ Review dated March 19, 2024, in DARRTS) contains an updated Labeling Review to indicate that all labeling revisions and recommendations were addressed by the Applicant. For all other individual discipline reviews for this NDA refer to OPQ Review dated March 19, 2024. Also, the number for the dissolution PMC (as it will appear in the NDA action letter) is now available and indicated above (the Applicant's agreement to the finalized PMC description and timelines, as above, was provided in the March 22, 2024, amendment).

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate with QPAs**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

Refer to the Drug Product Review (*Lifecycle Management Considerations*)

CHAPTER IV: LABELING (*Update*)

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	216483
Assessment Cycle Number	1
Drug Product Name	185 mg Pivmecillinam

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	
Carton Labeling	Adequate	

Labeling is provided for a 9-count package containing 1 blister sheet containing 9 tablets and a 50-count package containing 5 blister sheets of 10 tablets each. Both packaging configurations are made of the same materials and there are no differences in the manufacturing process between the two packs. All the comments and recommendations listed in the Labeling Review dated March 19, 2024, were addressed adequately.

Brief Description of Outstanding Issues: n/a

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, SDN 1	10/24/23	Carton and container label, USPI
0010, SDN 10	12/19/23	USPI
0026, SDN 26	2/7/24	Updated PI and carton/container labels
0029, SDN 29	2/9/24	Updated PI
0050, SDN 50		Updated container labels
0056, SDN 56	4/18/2024	Updated PI
0057, SDN 57	4/19/2024	Updated carton labels

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Inadequate	Strength should be in terms of the parent base

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item 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)
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).[6]	Inadequate	(b) (4) Drug product strength should be in terms of the free form.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	Adequate	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Inadequate*

See edits in red above. Drug product strength should be updated to be in terms of the free form instead of the hydrochloride salt.

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

Item	Item 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 and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and*	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item 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)
discoloration prior to administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] 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	

Assessment: *Inadequate*

See revisions above in red.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

[redacted]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item 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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	Strength should be revised to reflect the free form of the API. (b) (4) (b) (4)
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.	Inadequate	See edits above.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	

Assessment: *Inadequate*

See edits above in red.

1.2.3 Section 11 (DESCRIPTION)[14]

11. DESCRIPTION

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item 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 form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	See edits in red above
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)" [§ 201.57(c)(12)(i)(C)].	Inadequate	See edits in red above
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	See edits in red above
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item 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)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	See edits in red above
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (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").	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 2).	N/A	

Assessment: *Inadequate*

See edits in red above.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Inadequate	Strength to be updated in line with the USP Salt Policy. (b) (4)
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Tablets per blister sheet specified but not number of sheets. See edits above.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Inadequate	NDC code not present and not established

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item 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)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	
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." [§ 201.57(c)(17)(iv)]	Adequate	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex.*	N/A	

Item	Item 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)
Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Inadequate	Not present. See edits above.

Assessment: *Inadequate*

See edits in red above.

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Manufactured for: UTILITY therapeutics Ltd, UK
Manufactured by: Recipharm Strängnäs AB, Mariefredsvägen 35, S-645 41 Strängnäs, Sweden
Distributed by: UTILITY therapeutics Ltd, UK

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	

Assessment: *Adequate*

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

No additional patient labeling submitted.

Assessment: *Adequate*

No additional patient labeling provided

3.0 CONTAINER AND CARTON LABELING[24]

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

[24] Carton and Container Labeling Resources

(b) (4)

[redacted]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	No	Tablets packaged in individual blisters. Total count on outside of the carton.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	No	Acceptable to only be on the carton label
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	Not present on blister sheet. Acceptable.
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	No	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	Not present on blister sheet. Acceptable.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-	N/A	Choose an item.	

[27] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Choose an item.	Not applicable for oral products
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	No	Not present on blister sheet. Acceptable.
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	Not present on blister sheet. Acceptable.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	No	Not present on blister sheet. Acceptable.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
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.[30]	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*

[30] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Edits and comments will be communicated to the applicant via OND.

Primary Labeling Assessor Name and Date: Jessica Zarenkiewicz

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

Jessica Zarenkiewicz

Digitally signed by Jessica Zarenkiewicz
Date: 4/23/2024 07:41:01AM
GUID: 6239e6b2006583184e2eea406208dd4f

Dorota Matecka

Digitally signed by Dorota Matecka
Date: 4/23/2024 08:05:14AM
GUID: 508173530000859092c69506374d0011

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/

DOROTA M MATECKA
04/23/2024 09:27:15 PM

NDA Executive Summary

1. Application/Product Information

NDA Number.	216483		
Applicant Name	Utility Therapeutics Ltd		
Drug Product Name	PIVYA (pivmecillinam) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	185 mg		
Route of Administration	Oral		
Maximum Daily Dose	555 mg pivmecillinam (one tablet three times daily)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible *E.coli, Proteus mirabilis and Staphylococcus saprophyticus.*		
Drug Product Description	The proposed drug product is an immediate release film coated tablet for oral administration. The proposed tablet is a white, circular-shaped, film-coated tablet with a letter "P" (b) (4) on one side and blank on the other, which contains (b) (4) in addition to 200 mg of pivmecillinam hydrochloride (200 mg pivmecillinam hydrochloride corresponds to 185 mg pivmecillinam). The proposed commercial container closure system is a single-dose (b) (4) (b) (4) aluminum/ (b) (4) aluminum blister; each blister card contains ten (10) 185-mg tablets.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20 °C -25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Raymond Frankewich	Katherine Windsor
	Drug Product/ Labeling	Jessica Zarenkiewicz	Dorota Matecka
	Manufacturing	Jiao Yang	Nathan Davis
	Biopharmaceutics	Jing Li	Elsbeth Chikhale
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	

2. Final Overall Recommendation **Approval with QPAs (*pending labeling revisions*)**

3. Action Letter Information

a. Expiration Dating:

Store PIVYA tablets at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Store and dispense tablets in the unit-dose blisters.

b. Additional Comments for Action

The following Post-Marketing Commitment (PMC) should be included in the action letter:

PMC XXXX-X

Conduct studies and generate data to finalize the regulatory dissolution specification (method and acceptance criterion) for the drug product (pivmecillinam tablets, 185 mg) to be used at batch release and for stability studies.

Timelines:

Interim Report: 10/2024
Final Report: 05/2025

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substance (pivmecillinam hydrochloride) and the drug product (pivmecillinam tablets). The majority of the CMC information and data for pivmecillinam hydrochloride drug substance were provided via a reference to a Type II DMF (b) (4); the overall drug substance information submitted in the DMF, and the NDA was found adequate (refer to the Drug Substance review, below). In response to the FDA question regarding the USAN status of the pivmecillinam hydrochloride name, the Applicant has provided a confirmation that both names, pivmecillinam and pivmecillinam hydrochloride, have been adopted by the USAN Council (refer to the amendments dated February 28 and March 5, 2024). In addition, all comments, and requests for additional information, identified during the NDA review by the Drug Product and Manufacturing reviewers have been adequately addressed and resolved (for details refer to the Drug Product, and Manufacturing reviews, below). The currently proposed commercial blister card is not perforated; therefore, DMEPA has recommended adding a grid line to the blister sheet label to aid cutting while dispensing the correct number of tablets. (b) (4) From the Biopharmaceutics perspective, limited information was provided regarding the dissolution method development for the proposed commercial drug product. Therefore, the proposed dissolution method and acceptance criteria have been found acceptable on an interim basis with additional dissolution studies to be performed via a PMC study (as indicated above). The manufacturing and testing facilities have been found acceptable and an overall “Approve” recommendation for this NDA was entered in Panorama by the Office of Pharmaceutical Manufacturing Assessment on February 6, 2024. Several labeling revisions have been recommended in the Product Quality related sections of the Prescribing information (PI) as well as in the container label and carton labeling (e.g., properly displaying the drug product name and strength along with the salt equivalency statement). These comments have been conveyed to the NDA review team but have not been conveyed to or addressed by the Applicant. Therefore, the overall approvability recommendation for this NDA by the Office of Pharmaceutical Quality (OPQ) is *Approval with QPAs (pending labeling revisions)*. *An Addendum to this review will capture the final revisions to the various parts of labeling*.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	***Pending***
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate with QPAs**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

Refer to the Drug Product review (*Lifecycle Management Considerations*)

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	216483
Assessment Cycle Number	1
Drug Product Name	185 mg Pivmecillinam

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Inadequate	
Carton Labeling	Inadequate	

Brief Description of Outstanding Issues: See comments at the end of the review. Edits to the PI and comments regarding the carton and container closure will be communicated via OND. Labeling negotiations remain ongoing and are to be resolved by the PDUFA date.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, SDN 1	10/24/23	Carton and container label, USPI
0010, SDN 10	12/19/23	USPI
0026, SDN 26	2/7/24	Updated PI and carton/container labels
0029, SDN 29	2/9/24	Updated PI

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Inadequate	Strength should be in terms of the parent base

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item 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)
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).[6]	Inadequate	(b) (4) . Drug product strength should be in terms of the free form.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	Adequate	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Inadequate*

See edits in red above. Drug product strength should be updated to be in terms of the free form instead of the hydrochloride salt.

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

Item	Item 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 and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and*	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item 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)
discoloration prior to administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] 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	

Assessment: *Inadequate*

See revisions above in red.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

[redacted]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item 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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	Strength should be revised to reflect the free form of the API. (b) (4) (b) (4)
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.	Inadequate	See edits above.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	

Assessment: *Inadequate*

See edits above in red.

1.2.3 Section 11 (DESCRIPTION)[14]

11. DESCRIPTION

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item 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 form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	See edits in red above
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)" [§ 201.57(c)(12)(i)(C)].	Inadequate	See edits in red above
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	See edits in red above
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item 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)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	See edits in red above
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (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").	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 2).	N/A	

Assessment: *Inadequate*

See edits in red above.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Inadequate	Strength to be updated in line with the USP Salt Policy. (b) (4)
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Tablets per blister sheet specified but not number of sheets. See edits above.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Inadequate	NDC code not present and not established

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item 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)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	
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." [§ 201.57(c)(17)(iv)]	Adequate	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex.*	N/A	

Item	Item 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)
Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Inadequate	Not present. See edits above.

Assessment: *Inadequate*

See edits in red above.

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Manufactured for: UTILITY therapeutics Ltd, UK
Manufactured by: Recipharm Strängnäs AB, Mariefredsvägen 35, S-645 41 Strängnäs, Sweden
Distributed by: UTILITY therapeutics Ltd, UK

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	

Assessment: *Adequate*

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

No additional patient labeling submitted.

Assessment: *Adequate*

No additional patient labeling provided

3.0 CONTAINER AND CARTON LABELING[24]

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

[24] Carton and Container Labeling Resources

3.2 Carton Labeling

(b) (4)

[redacted]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	No	Tablets packaged in individual blisters. Total count on outside of the carton.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	No	Acceptable to only be on the carton label
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	Not present on blister sheet. Acceptable.
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	No	Expiry dating should be indicated on the carton in addition to the blister sheet.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	Not present on blister sheet. Acceptable.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose,	N/A	Choose an item.	

[27] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Choose an item.	Not applicable for oral products
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	No	Not present on blister sheet. Acceptable.
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	Not present on blister sheet. Acceptable.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	No	Not present on blister sheet. Acceptable.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
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.[30]	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Inadequate*

1. The drug product name and strength presentation should be revised to properly display the established name, pivmecillinam tablets, with the strength

[30] USP General Notices 3.20 Indicating Conformance

separated from the name, e.g., "PIVYA (pivmecillinam) tablets, 185 mg. The phrasing "film-coated" should be removed.
2. Add the expiry and lot number to the outside of the carton.
3. Barcodes should be present on each blister.
4. The salt equivalency statement should be removed from the front panel of the carton and the blister sheets. The salt equivalency statement should be present only on the side panel of the carton.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Edits and comments will be communicated to the applicant via OND.

Primary Labeling Assessor Name and Date: Jessica Zarenkiewicz

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

Jessica Zarenkiewicz

Digitally signed by Jessica Zarenkiewicz
Date: 3/19/2024 08:48:49AM
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Dorota Matecka

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Date: 3/19/2024 12:43:51PM
GUID: 508173530000859092c69506374d0011

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	216483
Assessment Cycle Number	1
Drug Product Name/ Strength	PIVYA™ (pivmecillinam) Tablets/ 185 mg[1]
Route of Administration	Oral
Applicant Name	UTILITY Therapeutics Ltd
Therapeutic Classification/ OND Division	Anti-Infectives (DAI)
RLD/RS Number	N/A
Proposed Indication	Indicated for the treatment of adults with uncomplicated urinary tract infections (uUTI) caused by susceptible (b) (4) and *Staphylococcus saprophyticus*.

Assessment Recommendation: **Adequate**
Adequate with Post-Marketing Commitments (PMC 4603)

Assessment Summary:

UTILITY therapeutics Ltd. is submitting this 505(b)(1) NDA, seeking approval of pivmecillinam tablets for the treatment of uncomplicated urinary tract infections. Pivmecillinam hydrochloride (HCl), is an oral prodrug of mecillinam (amdinocillin), a β-lactam antibiotic with bactericidal activity against a targeted spectrum of Gram-negative bacteria including Enterobacterales. Currently, pivmecillinam HCl tablets are approved in Canada, Europe, some Asian countries, and some African countries. The key/pivotal clinical efficacy and safety studies supporting the approval of this NDA are from the submitted literature reports.

This Biopharmaceutics review is focused on the evaluation of the following aspects:

- Dissolution method and acceptance criterion
- Bridging between the clinical formulations used in the literature reported studies and the to-be-marketed formulation

[1] The strength of the drug product is expressed based on base form as pivmecillinam 185mg, which is equivalent to pivmecillinam HCl 200 mg which was referred to in the submission and this review.

Dissolution method and acceptance criterion. The drug substance exhibits high solubility in pH 1.2 and 4.5, but BCS "high solubility" criterion is not met due (b) (4) The Applicant has been using the same dissolution method since 1981 for this immediate release drug product on the out-of-US market. Based on the limited dissolution method development information available, the proposed dissolution method is acceptable on an interim basis. The Applicant proposed dissolution acceptance criterion of "≥ (b) (4)%(Q) in 30 min" is too permissive and thus not acceptable, and FDA recommends the Applicant tighten the acceptance criterion to "Q=(b) (4)% in 30 min" on an interim basis. Therefore, the following dissolution method and acceptance criterion are acceptable only on an interim basis. To support the approval of the final dissolution test, the Applicant is requested to submit dissolution data for the commercial batches (b) (4) (b) (4) (b) (4)

Apparatus	USP apparatus 2 (paddle)
Rotation/ agitation speed	50 rpm
Medium	simulated gastric fluid without pepsin (2 g/L NaCl adjusted to pH 1.2)
Medium volume	900 mL
Temperature	37.0 °C ± 0.5 °C
FDA Recommended Acceptance Criterion	Q=(b) (4)% at 30 min

In addition, there are the following pending issues that need to be resolved as Post-Marketing Commitments:

1. (b) (4)
2. (b) (4)

The detailed PMC comments[2] are included in Appendix II, and the Applicant agreed to the PMC comments on 02/27/2024[3], and updated the Drug Product Specifications Accordingly[4].

Formulation Bridging. The key/pivotal clinical efficacy and safety studies supporting the approval of this NDA are from the submitted literature reports. Formulations used in the key studies (except for the Vik 2018 study) differ from the currently proposed formulation in drug product manufacturing site and the inactive ingredients used (b) (4) (b) (4), (b) (4) (b) (4) Though no in vivo bioequivalence study was conducted comparing these formulations, the bridging between the clinical formulations used in the literature reported studies and the currently proposed formulation is supported by the following justifications:

- The (b) (4) The changes in the (b) (4) (b) (4) are minor and are unlikely to impact the dissolution or bioavailability of the drug product.
- Comparative disintegration time and dissolution data are submitted to support similar disintegration and drug release.
- The drug substance is highly soluble at acidic pH, and the in vivo Tmax following oral administration is about 1.0 hr. (b) (4) (b) (4) (b) (4).
- The Applicant noted that the formulations have been introduced to the global markets over the years and no report of safety or efficacy concerns related to the changes in the formulation is known.

The Applicant proposed (b) (4) (b) (4)

Overall, NDA 216483 for Pivmecillinam Tablets, 185 mg, is recommended for approval, with post-marketing commitments (PMC # 4603, See APPENDIX II).

[2] NDA 216483 IR about PMC. https://panorama.fda.gov/internal/document/preview?versionID=65d913e700b167d51d4006f21155b97d&ID=65d90fe800f2a440a31a65ef5f3e5ada

[3] Response submitted on 02/27/2024 to IR dated 02/23/2024. \\CDSESUB1\EVSPROD\nda216483\0036\m1\us\111-information-amendment\response-ir-feb23.pdf

[4] NDA 216483 Drug Product Specification. \\CDSESUB1\EVSPROD\nda216483\0036\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p5-contr-drug-prod\32p51-spec\32p51-specifications.pdf

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution	medium	(b) (4)	low	The dissolution specifications are acceptable on an interim basis (b) (4) (b) (4) Applicant will address the pending issues post marketing via PMC.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original NDA- SDN 1	10/24/2024
Response to IR- SDN 12	12/19/2023
Response to IR- SDN 18	01/10/2024
Response to IR- SDN 20	01/18/2024
Response to IR- SDN 23	01/31/2024
Response to IR- SDN 27	02/08/2024
Response to IR- SDN 31	02/14/2024
Response to IR about PMC- SDN 36	02/27/2024

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first cycle of review.

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*:

The following specific issues were identified and need to be resolved through a Post-Marketing-Commitment (PMC):

1. The proposed dissolution method [USP Apparatus 2 at 50 rpm, 900 ml of simulated gastric fluid without pepsin (2 g/L NaCl adjusted to pH 1.2)] and the recommended/revised acceptance criterion [Q=(b) (4)% in 30 min] has been accepted only "on an interim basis".

(b) (4)

B.1 BCS DESIGNATION

Assessment: Not Applicable.
BCS designation is not applicable, due to the significant degradation in neutral and basic pH. The solubility is pH-dependent with high solubility in pH 1.2 and 4.5.

Solubility: The Applicant noted that 400 mg pivmecillinam HCl (the proposed to-be-marketed strength is 200 mg) is dissolved visually within 1 min at 37°C in pH 1.2 and pH 4.5. Degradation to (b) (4) occurs at pH (b) (4) and (b) (4) and

(b) (4)

Permeability: No permeability data is available. Pivmecillinam is the pro-drug of mecillinam, that is rapidly hydrolyzed in the body to mecillinam, the active antibacterial agent. As per the proposed US package insert[6], "the absolute bioavailability of mecillinam after orally administered pivmecillinam is estimated to be around 40% for a 185 mg pivmecillinam tablet".

Dissolution: See Section B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Acceptable on an interim basis with PMC.

[5] Solubility study report. \\CDSESUB1\EVSPROD\nda216483\0012\m1\us\111-information-amendment\attach-1.pdf
[6] Proposed USPI. \\CDSESUB1\EVSPROD\nda216483\0023\m1\us\114-labeling\draft\labeling\pivmecillinam-uspi.pdf

DISSOLUTION METHOD:

Since 1977, disintegration test has been implemented for 200 mg pivmecillinam tablet. The dissolution test was introduced since 1981, and the same dissolution method is proposed in the current NDA submission, though different method names was referred to during different time periods (9-697 for LEO Pharma and S1010 for Recipharm).

The currently proposed dissolution method and acceptance criterion are as follows:

Table 1. The Proposed Dissolution Method and Acceptance Criterion

Apparatus	USP apparatus 2 (paddle)
Rotation/ agitation speed	50 rpm
Medium	simulated gastric fluid without pepsin (2 g/L NaCl adjusted to pH 1.2)
Medium volume	900 mL
Temperature	37.0 °C ± 0.5 °C
Applicant Proposed Acceptance criterion	≥ (b) (4)% (Q) after 30 min
FDA Recommended Acceptance Criterion	Q (b) (4)% at 30 min

(b) (4)

[redacted]

[7] Response to IR dated 1/24/2024. \\CDSESUB1\EVSPROD\nda216483\0023\m1\us\111-information-amendment\response-ir-jan24.pdf

(b) (4)

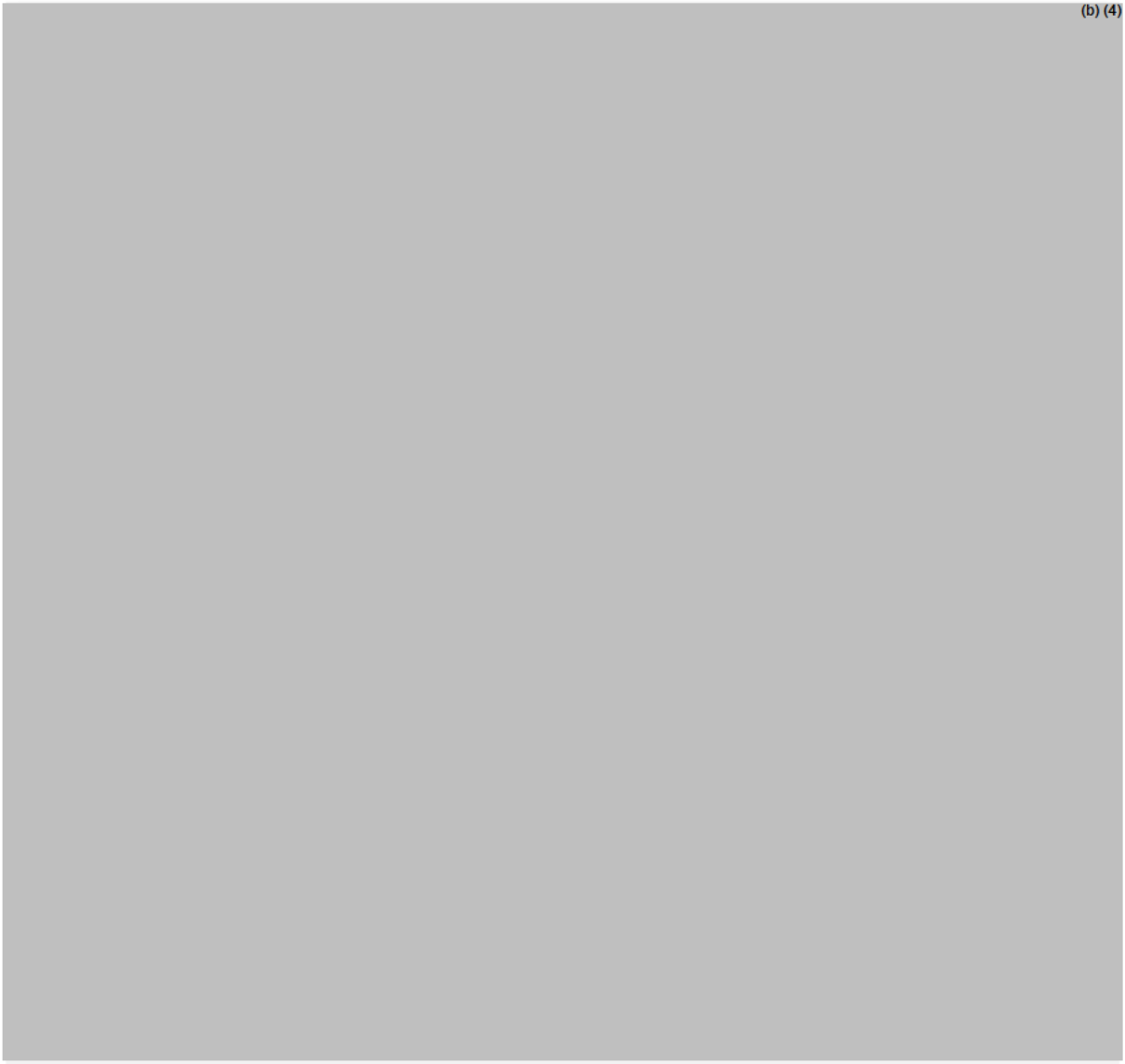
Dissolution Test with Standard Method as Per 2018 Guidance

Although the BCS guidance may not be applicable to the proposed drug product due to the (b) (4) the drug substance demonstrated high solubility in pH 1.2 and 4.5, (b) (4) (b) (4) Therefore, the Applicant was advised in IR dated 01/24/2024 to collect dissolution data by using the standard dissolution method recommended in the 2018 Guidance for Industry on 'Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances'. In the response dated 02/14/2024, the Applicant provided dissolution data at pH 1.2 under three different testing conditions:

Table 3. pH 1.2 Dissolution Testing Conditions[9]

(b) (4)

[8] Pharmaceutical development report, Page 32. \\CDSESUB1\EVSPROD\nda216483\0001\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p2-pharm-dev\32p22-drug-product.pdf
[9] Response to IR dated 2/9/2024. \\CDSESUB1\EVSPROD\nda216483\0031\m1\us\111-information-amendment\response-ir-feb9.pdf



(b) (4). Considering the high solubility of the drug substance in acidic pH, and the historical use of the proposed dissolution method, the proposed dissolution method is acceptable as a QC method, but only on an interim basis (see more discussions under DISSOLUTION ACCEPTANCE CRITERION).

Discriminating Ability of the Dissolution Method

The Applicant noted that a correlation between disintegration of the tablet and hardness (b) (4) of the tablet was established, and disintegration is a prerequisite for dissolution, hence the Applicant concluded the discriminating ability of the dissolution method. However, no experimental data were submitted to support the discriminating ability of the method.

Stability Indicating Property of the Dissolution Method

A stressed stability study (Study 3) with high humidity and high temperature was conducted on unpackaged tablets. At conditions with high temperature or high humidity, a trend of decrease in dissolution was observed as shown in Figure 2.

Figure 2. Stress testing dissolution data (stability study 3)

Based on the information available, the proposed dissolution method is acceptable on an interim basis for quality control of the drug product at batch release and during stability.

DISSOLUTION ACCEPTANCE CRITERION

The Applicant proposed a dissolution acceptance criterion of "≥ (b) (4)% (Q) after 30 min"[10]. There are no dissolution data for the clinical lots available, and some of the clinical lots had a formulation composition that is different from the to-be-marketed formulation (See B.12 Bridging of Formulations). Therefore, the following dissolution data are considered when evaluating the dissolution acceptance criterion:

Batch Analysis Data. Data in Module 3.2.P.5.4 showed that 4 batches of 200 mg tablets that were manufactured in Aug. to Nov. 2015 showed 86% to 90% dissolution in average within 30 min[11].

Stability Data. The Applicant submitted 4 sets of stability data and 3 sets among them contained dissolution data.

- Stability study 1[12]: Dissolution was not carried out at Time zero (T-0) but was conducted at the subsequent time points. The three tested batches

[10] Drug product specification. \\CDSESUB1\EVSPROD\nda216483\0027\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p5-contr-drug-prod\32p51-spec\32p51-specifications.pdf
[11] Batch Analyses. \\CDSESUB1\EVSPROD\nda216483\0001\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p5-contr-drug-prod\32p54-batch-analys\32p54-batch-analyses.pdf
[12] Stability Data- Study 1. \\CDSESUB1\EVSPROD\nda216483\0001\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p8-stab\32p83-stability-data-study-1.pdf

were manufactured in Nov. to Dec. 2013. The long-term stability data showed more than 90% dissolution in 30 min for all batches at stability pulling time points from 3-month up to 36-month. The dissolution data at the 15-min time point was also reported, and it showed around 90% dissolution for all batches.

- Stability Study 2[13]: The tested batch RS-393 was manufactured in Nov. 2020, and packed in the container closure system intended for the US market. The long-term stability data showed that average dissolution was 84-88% at the 30-min time point.
- Stability Study 3: This study presents the results of the stress testing of the drug product. The data were not considered for setting of the acceptance criterion.
- Stability Study 4: No dissolution data was collected in this study.

Multi-Time Point Dissolution Data. The following multi-time point dissolution profile data are extracted from the Stability Study Report, Drug Product Development Report, and IR responses.

Table 6. Summary of Multi-time point Dissolution Data Submitted

Batch #	Date of Manufacture	Time points (minutes) 5	10	15	20	25	30	Source
26002 (b) (4) 26214 (b) (4)	Dec. 2013	(b) (4)						Stability study 1. (Data presenting the range of the average dissolution collected at long-term stability study pulling time points of 3-month to 36-month
26248 (b) (4) 26213 (b) (4)	Nov. 2013							
26308 (b) (4) 26305 (b) (4)	Dec. 2013							
92013	May 2007							Product Development Report/ Page 30
92014	May 2007							
92015	May 2007							
96253	Mar. 2010							Product Development Report/ Page 33
RS-393	Nov. 2020							Response (submitted on 1/31/2024) to FDA IR dated 1/24/2024
RS-463	Aug. 2023							Response (submitted on

[13] Stability Data- Study 2. \\CDSESUB1\EVSPROD\nda216483\0001\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p8-stab\32p83-stability-data-study-2.pdf

								2/14/2024) to FDA IR dated 2/9/2024

It is observed that most batches exhibited rapid dissolution with more than 85% dissolution in 30 minutes. However, the recently manufactured batch RS-463 (manufactured in 2023) exhibited significantly slower dissolution compared to other batches that were manufactured in earlier years (2007 and 2013). Based on the limited dissolution data available, an acceptance criterion of "Q (b) (4) % in 30 min" will be recommended on an interim basis. It is noted that batch RS-463 is not able to meet the recommended acceptance criterion (b) (4) (b) (4) Therefore, the Applicant is requested through a Post-Marketing Commitment (PMC) to (1) submit dissolution data for (b) (4) commercial batches to be manufactured (b) (4) to support the approval of the final dissolution test; (b) (4) (b) (4)

(b) (4)

(b) (4)

[14] Response to IR dated 2/5/2014. \\CDSESUB1\EVSPROD\nda216483\0027\m1\us\111-information-amendment\response-ir-feb5.pdf

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA ***(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)***

Assessment: Not Applicable.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Not Applicable.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: Not Applicable.

IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: Not Applicable.

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: Not Applicable.

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: Not Applicable.

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: Not Applicable.

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: Not Applicable.

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: Not Applicable.

[15] Pharmaceutical development report, Page 33. \\CDSESUB1\EVSPROD\nda216483\0001\m3\32-body-data\32p-drug-prod\pivmecillinam-tablet-leo-laboratories-ltd\32p2-pharm-dev\32p22-drug-product.pdf

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate.

Pivmecillinam was originally formulated in 1975 as a hard gelatin capsule containing 200 mg pivmecillinam hydrochloride however was never launched commercially. In 1977, the drug product formulation was changed to a 200 mg film-coated tablet, and the tablet was launched by LEO Pharma. Since then, there have been multiple changes in the formulation and composition of the drug product, and the manufacturing sites throughout the development process and marketing history. Briefly,

- In 1981, the drug product was re-formulated to include (b) (4) (b) (4). From 1981 to present no changes were introduced (b) (4)
- Between 1981 and 1998 (b) (4) (b) (4), (b) (4).
- In 2000, the manufacture of pivmecillinam tablets was transferred from LEO Pharma A/S site Ballerup, Denmark to LEO Laboratories Ltd., Dublin, Ireland. (b) (4) (b) (4)
- In 2006, the manufacture of pivmecillinam tablets was transferred from LEO, Dublin, Ireland to the current manufacturing site, Recipharm, Strängnäs, Sweden. (b) (4) (b) (4)
- The current formulation of 200 mg strength, manufactured by Recipharm, Sweden since 2006, is the final formulation for pivmecillinam tablets 200 mg proposed for the US market.
- Based on the Facility and Process review, there are differences in manufacturing process between the clinical batches and the to-be-market batches. However, "process validation was performed to justify the site transfer and the (b) (4), all the IPCs and drug product CQAs are confirmed equivalent/comparable".[16]

The composition Tables for all these formulations are included in APPENDIX I.

The following diagram provides this reviewer's summary of the changes and the in vivo bridging information (in green) based on the submission. The publications containing the pivotal clinical studies are depicted in red.

[16] NDA 216483 Facility and Process Review.
https://panorama.fda.gov/internal/document/preview?versionID=65ca41660009bbe536bca1f2d080d57e&ID=65ca41660009bbe4ace7cf6e7777289d

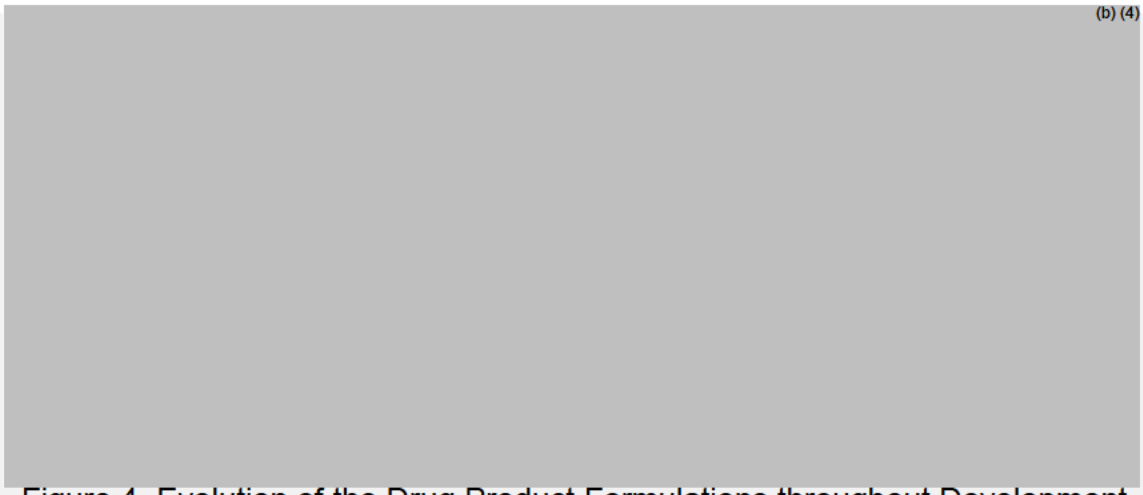


Figure 4. Evolution of the Drug Product Formulations throughout Development and Marketing

The Clinical Division has identified the following four key/pivotal clinical efficacy and safety studies from the submitted literature reports: *Menday 2000, Ferry 2007, Vik 2018, and Nicolle 2002*. Based on the time of manufacturing of the trial medication, the dates on Case Report Forms, the clinical Study reports, the Applicant identified the formulations used in each individual key clinical studies as shown in Table 7.

Table 7. Formulations Used in the Key Clinical Efficacy and Safety Studies[17]

Literature/Trial	Formulation, strength, year, and manufacturer	To-be-marketed Formulation used (Yes/No)
Menday 2000	1981 formulation, 200 mg, 1980-1983, (b) (4)	No
Ferry 2007	1981 formulation, 200 mg, Jan 1994, LEO Pharma A/S, Denmark	No
Vik 2018	2006 formulation with (b) (4), 200mg, 2010-2016, Recipharm Strängnäs, Sweden	Yes, (b) (4) (b) (4)
Nicolle 2002	1998 formulation, June 1998, LEO Pharma A/S, Denmark	No

The key studies are included in the Figure 4 diagram (in red) next to the formulation that was used in the individual study.
Vik 2018 used the same formulation manufactured at the same site as the currently proposed formulation.
Formulations used in other key studies differ from the currently proposed formulation in manufacturing site and the inactive ingredients used (b) (4) (b) (4) (b) (4) (b) (4) As per SUPAC-IR guidance, though manufacturing site change can be supported by in vitro dissolution test, (b) (4)

[17] Based on the IR Response submitted on 1/10/2024. \\CDSESUB1\EVSPROD\nda216483\0018\m1\us\111-information-amendment\response-ir-dec21.pdf

(b) (4). The Applicant confirmed that no bioequivalence study was conducted when the changes were introduced. Instead, the following justifications were submitted to support the bridging between the formulations.

1) The key clinical studies were conducted with formulations manufactured post-1981. Since 1981, the changes in composition were considered minor, due to (b) (4) (b) (4) (b) (4) (b) (4)

5) The 1977 formulation, which has a different (b) (4)) from the currently proposed formulation has similar bioavailability in comparison to the 1981 formulation (b) (4) based on Office of Clinical Pharmacology assessment.
6) The current formulation (same as 2006 formulation) showed similar disintegration time as the 1981 formulation.

Table 8. Disintegration time for 200 mg formulations

Tablets 200 mg	1977 formulation	1981 formulation	2006 formulation
Disintegration	Mean 10.96 min (n=18) Range (b) (4)	Mean 4.43 min (n=18) Range (b) (4)	≤ 5 min (release data of three batches) (range: (b) (4) min)

7) The comparative dissolution data were submitted, which showed very rapid dissolution for all formulations (>85% in 15 min), though 2006 formulation showed slightly slower dissolution, possibly due to (b) (4).

Table 9. Comparative dissolution (pH 1.2) for 200mg tablets

Dissolution	1977-formulation			1981-formulation			2006-formulation for US market (three batches)		
	Time	Median (%)	Range (%)	Time	Median (%)	Range (%)	Time	Mean (%)	Range (%)
Data	5 min	38	(b) (4)	5 min	101	(b) (4)	5 min	nt	nt
	10 min	77		10 min	102		10 min	89.9 87.3 82.9	(b) (4)
	15 min	97		15 min	102		15 min	nt	
	20 min	98		20 min	102		20 min	94.6 93.1 88.5	
	30 min	98		30 min	nt		30 min	96.3 94.8 90.9	

nt = 'not tested'

8) The drug substance is highly soluble at acidic pH. The in vivo Tmax following oral administration is about 1.0 hr, indicating absorption likely takes place (b) (4)
9) The Applicant noted that the formulations have been introduced to the global markets over the years and no report of safety or efficacy concerns related to the changes in the formulation is known. Also, no recall after introduction of the (b) (4) in 2006 was initiated, and the general safety profile of the product as well as the efficacy have been acceptable on the global markets.

Overall, the Applicant's justifications are found acceptable, and the bridging between the formulations used in the key clinical studies and the to-be-marketed formulations proposed in the original NDA submission is established.

(b) (4)

B. 13 BIOWAIVER REQUEST

Assessment: Not Applicable.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: Not Applicable.

Post-Approval Commitments

The Applicant agreed to the following Post-Marketing Commitment on 02/27/2024[18]:

*The following PMC **Initial** and **Final** Reports should be submitted within **6 months** (Initial Report) and **13 months** (Final Report), from the NDA's action date, under Prior Approval Supplements (PAS) to your NDA.*

Initial Report:
The initial report should include the following:

(b) (4)

Final Report:

The final report should provide

(b) (4)
(b) (4)

[18] Response submitted on 02/27/2024 to IR dated 02/23/2024. \\CDSESUB1\EVSPROD\nda216483\0036\m1\us\111-information-amendment\response-ir-feb23.pdf

Lifecycle Management Considerations

Not Applicable.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

See PMC comments.

Primary Biopharmaceutics Assessor's Name and Date: Jing Li, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Elsbeth Chikhale, Ph.D.

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Jing Li

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Date: 2/27/2024 08:36:39PM
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