

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219878Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

NDA Executive Summary – Original NDA

1. Application/Product Information

NDA Number.	219878		
Applicant Name	AstraZeneca AB		
Drug Product Name	BAXFENDY (baxdrostat)		
Dosage Form.	Tablet		
Proposed Strength(s)	1 mg and 2 mg		
Route of Administration	Oral		
Maximum Daily Dose	2 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Baxdrostat is an aldosterone synthase inhibitor indicated (b) (4) for the treatment of hypertension, to lower blood pressure in adults who are not adequately controlled on other agents. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions		
Drug Product Description	film-coated tablets: • 1 mg pink, biconvex, round, film-coated tablets with “BX” debossed on one side and “1” on the other side. • 2 mg yellow, biconvex, round, film-coated tablets with “BX” debossed on one side and “2” on the other side.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Mitchell McCloskey	Zhengfu Wang



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

	<i>Drug Product/ Labeling</i>	George Ward	Theodore Carver
	<i>Manufacturing</i>	Allison Aldridge	Aditi Thakur
	<i>Biopharmaceutics</i>	Rajesh Savkur	Haritha Mandula
	<i>Microbiology</i>	N/A	
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Oluwafunmike Ajomale	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the drug product when stored at 20°C to 25°C

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

AstraZeneca AB has submitted an NDA in accordance with 505(b)(1) of the Federal Food, Drug, and Cosmetics (FD&C) Act seeking approval of baxdrostat, an aldosterone synthase inhibitor indicated (b) (4) for the treatment of hypertension, to lower blood pressure in adults who are not adequately controlled on other agents. The Applicant relies on the results of a single pivotal Phase 3 study for approval. The



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

drug product is provided as 1 mg and 2 mg immediate-release, film-coated tablets. The OPQ review team included the drug substance, drug product, manufacturing/facilities, and biopharmaceutics review disciplines.

2) Drug Substance

Baxdrostat is a synthetic small molecule aldosterone synthase inhibitor manufactured by (b) (4)

(b) (4)

(b) (4). The characterization package (NMR, single-crystal XRD, HRMS, IR, elemental analysis, UV-vis, XRPD, GVS, DSC, TGA) is adequate to confirm the proposed structure and physical properties. The DS specification includes appearance, identity (FT-IR), assay (LC), organic impurities (LC), and residual solvents (GC); after an IR, the unspecified impurity limit was revised from NMT (b) (4)

(b) (4) The specification and control strategy are adequate. Stability data from three primary batches at pilot scale support a (b) (4) retest period when stored (b) (4)

(b) (4).

3) Drug Product

Baxdrostat tablets are immediate-release, round, biconvex, film-coated tablets (pink for 1 mg, yellow for 2 mg) with core excipients of anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate, coated (b) (4). The drug product specification covers appearance, identification (two orthogonal methods: LC retention time and UV), assay (b) (4), degradation products, (b) (4), disintegration, dissolution, and uniformity of dosage units per USP <905>. Three primary stability batches per strength (b) (4) were placed on stability in HDPE bottles; 12 months of long-term (30°C/75% RH) and 6 months of accelerated (40°C/75% RH) data are available, with the only change being (b) (4). Based on ICH Q1E, extrapolation of 12 months beyond the available data is appropriate, for a commercial a shelf life of 24 months

4) Manufacturing

Process - The proposed commercial manufacturing process employs

(b) (4)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03



(b) (4)

Facilities - A pre-approval inspection (PAI) was conducted April 7–10, 2026, at AstraZeneca AB (Södertälje, Sweden) and resulted in two observations related to deviation investigation adequacy and CAPA system effectiveness, both with acceptable corrective action plans. All other facilities are approvable based on previous inspection history. Therefore, the final facility recommendation is approval.

5) Biopharmaceutics

The biopharmaceutics review of baxdrostat tablets evaluated the BCS classification, in vitro dissolution methodology, disintegration testing, and product bridging. Baxdrostat is classified as a BCS Class 1 compound based on high solubility across the physiological pH range (1.2–6.8) and high permeability. The applicant proposed a non-Guidance-standard dissolution method using 0.01 N HCl (rather than the recommended 0.1 N HCl) with USP Apparatus 1 at 100 rpm, justified by superior sample solution stability at (b) (4). After multiple information request (IR) cycles, the agreed-upon dissolution acceptance criterion for stability is $Q =$ (b) (4) in 20 minutes, while a disintegration test (NMT (b) (4) per USP <701>) was accepted as the QC release test and stability surrogate. Bridging of the to-be-marketed (TBM) (b) (4) tablets to the Phase 1 and Phase 3 (b) (4) tablets was accomplished via in vitro dissolution profile comparisons demonstrating >85% dissolution in 15 minutes across physiological pH media, with no additional in vivo study required.

6) Quality Aspects of Labeling

The quality aspects of the carton and container labeling and prescribing information were found to be acceptable after comments/revisions were addressed.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None.

Comparability Protocols (PACMP): No
Comments: None.

Additional Lifecycle Comments: None.



Theodore
Carver

Digitally signed by Theodore Carver

Date: 5/01/2026 02:28:40PM

GUID: 5d963967007fd4bc3c9fab2a6c3eaded

51 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page



Title:	NDA IQA Template CHAPTER IV-LABELING
Document ID:	OPQ-ALL-TEM-0045
Effective Date:	18 Sep 2023 Revision: 00
Total Pages:	17



Template Revision: 03

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	219878
Assessment Cycle Number	#1
Drug Product Name	BAXFENDY (baxdrostat tablets)

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate (“N/A” otherwise)
Prescribing Information Labeling	Adequate	SD 1
Patient Information	N/A	N/A
Instruction for Use (IFU)	N/A	N/A
Container Labels	Adequate	SD 1
Carton Labeling	Adequate	SD 1

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, SD 1	9/17/2025	Original PI and labeling

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

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)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION



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 Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	Tradename BAXFENDY, conditionally approved
Route(s) of administration	Adequate	For oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	2026
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	1 mg and 2 mg
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	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored.” ⁷	Adequate	Not scored

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>

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 \(March 2013\)](#)

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)
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: *Adequate*

Highlights section is adequate with no edits beyond updating with approved trade name

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)	Adequate	

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>

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)

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)
and/or soft food ¹⁰ , storage conditions needed 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).	Adequate	Do not cut, crush or chew tablets
For parenteral products: include statement: <i>“Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”</i> ¹¹	N/A	
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 <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.”</i> ^x with x numerical citation to “OSHA Hazardous Drugs.”	N/A	

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](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Assessment: Adequate

Section 2 is adequate with DMEPA additional comment.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(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 FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Film-coated tablets
Strength(s) in metric system	Adequate	1 and 2 mg
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.	N/A	Not a salt
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	1 mg – pink round tablet with BX and 1 debossed on opposite sides 2 mg – yellow round tablet with BX and 2 debossed on opposite sides
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	Not scored
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	N/A	

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)
pharmacy bulk package and imaging bulk package (see USP <659>).		

Assessment: *Adequate*

Section 3 is adequate as is with no edits necessary.

1.2.3 Section 11 (DESCRIPTION)¹⁴



(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		

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

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)
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	Removed trade name from paragraph 1.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Tablet for oral administration
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)].	N/A	
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)].	Adequate	Film coating ingredients listed separately with the differentiating color component listed at the end.
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	N/A	

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).

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)
absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	Aldosterone synthase inhibitor.
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
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	None present
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: Adequate

Adequate with the changes listed.

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.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	

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)
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)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored.”	Adequate	Not scored
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.” 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	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)
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	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)
natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i> ²¹		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	

Assessment: Adequate

Adequate with the changes made in the SharePoint. DMEPA determined (b) (4) (b) (4) should not be included in section 16.

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.

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)

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

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*

2.0 PATIENT LABELING

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

None Provided

Assessment: Choose an item.

No IFU or Patient Guide present.

3.0 CONTAINER AND CARTON LABELING²⁴

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ [Carton and Container Labeling Resources](#)

3.1 Container Labels²⁵



3.2 Carton Labeling

No Carton proposed for packaging

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	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	Once updated with approved trade name
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁷	Adequate	1 mg and 2 mg

²⁵ Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

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

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 \(May 2022\)](#)

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Not required for oral use
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	Not a salt
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁸	Adequate	30 or 7 tablets
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	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, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	

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 Container Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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	Oral drug so not required
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	
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	
Linear Bar code [§ 201.25(c)(2)]. ²⁹	Adequate	Linear bar code needs to be added
Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Adequate	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	
“Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	

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 Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	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. ³⁰	N/A	
And others if space is available.	N/A	

Assessment of Carton Labels and Container Labeling: Adequate

Adequate with the addition of the linear bar code to the container label.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None with the above edits made.

Primary Labeling Assessor Name and Date: George Ward, Ph.D. 3/16/2026

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph.D.

³⁰ USP General Notices 3.20 Indicating Conformance

APPEARS THIS WAY ON ORIGINAL



George
Ward

Digitally signed by George Ward
Date: 3/17/2026 02:17:42PM
GUID: 6283b837000d5b5c50a91367cbb8637c



Theodore
Carver

Digitally signed by Theodore Carver
Date: 3/17/2026 02:20:36PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

41 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-219878-ORIG-1
Submission History	9/17/2025 (Sequence 0001): Original submission 1/12/2026 (Sequence 0018): Response to CMC Information Request 1/30/2026 (Sequence 0021): Response to CMC Information Request 2/26/2026 (Sequence 0023): Response to CMC Information Request 3/13/2026 (Sequence 0024): Response to CMC Information Request
Drug Product Name/ Strength	BAXFENDY™ (Baxdrostat) tablets, 1 mg and 2 mg
Route of Administration	Oral
Applicant Name	AstraZeneca Pharmaceuticals LP
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology (DCN)
Proposed Indication	Baxdrostat tablets are indicated (b) (4) for the treatment of hypertension, to lower blood pressure in adults who are not adequately controlled on other agents.
IND Number	IND-146112
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Haritha Mandula, Ph.D.
Assessment Recommendation	Adequate

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of BAXFENDY™ (Baxdrostat) tablets, 1 mg and 2 mg, a new molecular entity, potent, orally bioavailable small-molecule inhibitor of aldosterone synthase that is indicated (b) (4) for the treatment of hypertension, to lower blood pressure in adults who are not adequately controlled on other agents. NDA-219878-ORIG-1 was initially submitted to the Division of Cardiology and Nephrology (DCN) on 9/17/2025 under section 505(b)(1). The recommended (b) (4) dosage is 2 mg orally once daily, with or without food. Treatment with 1 mg once daily can be considered (b) (4)

Assessment Summary:

The Biopharmaceutics assessment focuses on evaluating (i) the *in vitro* dissolution method development, the *in vitro* dissolution data and the *in vitro* dissolution acceptance criterion, (ii) disintegration method, disintegration data and the disintegration acceptance criterion,

and (iii) the bridging data between the clinical and commercial/to-be-marketed drug products, the manufacturing sites and batch sizes.

- **In vitro dissolution method and acceptance criterion:**

The active pharmaceutical ingredient (API), baxdrostat, is a crystalline powder. The solubility data indicates that the drug substance exhibits a high solubility across the physiological pH range of 1.2–6.8 at 37 °C. The absolute bioavailability of baxdrostat at the 3 mg dose is 97.2%, and the *in vitro* permeability of baxdrostat in the Caco-2 monolayer model indicates that the $P_{app[A \rightarrow B]}$ for baxdrostat is ~2-fold higher than the $P_{app[A \rightarrow B]}$ of the high-permeability marker, minoxidil (10×10^{-6} cm/s). Thus, baxdrostat can be considered as a high-permeability drug substance. Based on the high-solubility and high-permeability of the API, in accordance with the May 2021 ICH *Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers*, baxdrostat has been designated as a BCS class 1 compound (IND-146112).

The *in vitro* dissolution method and acceptance criterion proposed by the Applicant for Quality Control (QC) of the drug product for the stability program differ from the *Guidance*-recommended¹ method and acceptance criterion. The proposed dissolution method exhibits limited discriminating ability towards (b) (4)

(b) (4) The proposed *in vitro* dissolution acceptance criterion is supported by the dissolution data of the exhibit/primary stability batches. The *in vitro* dissolution test implemented for the stability program would imply that the drug product would also satisfy the test specifications at release and ensure that the quality of the drug product is maintained at release and through stability. Based on the submitted information, the *in vitro* dissolution method and acceptance criterion as shown below in Table 1A are agreed upon by the FDA and the Applicant for the QC of Baxdrostat tablets, 1 mg and 2 mg, for the stability program.

Table 1A: Approved *in vitro* dissolution method and acceptance criterion for Baxdrostat tablets, 1 mg and 2 mg

Approved <i>in vitro</i> dissolution method for stability				Approved <i>in vitro</i> dissolution acceptance criterion for stability
Source	Apparatus	Medium/ Volume	Agitation speed/ Temperature	Q = (b) (4)% in 20 minutes
In-house	USP apparatus 1	Medium: 0.01 N HCl Volume: 500 mL	Speed: 100 rpm Temp: 37 °C	

- **Disintegration method and acceptance criterion:**

The Applicant proposed to implement a disintegration test for QC of the drug product at release and through stability. The disintegration test would be performed according to USP <701>, in purified water using discs. The justification for using disintegration test as a surrogate for dissolution for quality control for the drug product is based on

¹ Guidance for Industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances, August 2018

ICH Q6A and the criteria outlined in Decision Tree #7(1). In the responses to the Information Requests, the Applicant proposed a disintegration acceptance criterion of 'NMT (b) (4)'. The *in vitro* dissolution method exhibits limited discriminating ability towards (b) (4). Thus, the dissolution method with the acceptance criterion would not possess the ability to discriminate against (b) (4). However, the disintegration test/acceptance criterion of 'NMT (b) (4)' would ensure that a rapid (>85%) dissolution of the product is achieved in 15-minutes and maintain the quality of the drug product. In addition, the proposed in-process control (IPC) limit for (b) (4) (1 mg: (b) (4) and 2 mg: (b) (4)) would correspond to a maximum (b) (4) of (b) (4), a maximum disintegration time of (b) (4) seconds (i.e., (b) (4) minutes) and a mean dissolution of (b) (4)%. Thus, the Applicant's proposal to exclude the dissolution test at release but implement it for the stability program is found acceptable, which would minimize the manufacturing of batches with dissolution times that are slower compared to the target/optimal batches, and ensure that the quality of the drug product is maintained at release and through stability. Based on the submitted information, the disintegration method and acceptance criterion as shown below in Table 1B are agreed upon by the FDA and the Applicant for the QC of Baxdrostat tablets, 1 mg and 2 mg, at release and through the stability program.

Table 1B: Approved disintegration method and acceptance criterion for Baxdrostat tablets, 1 mg and 2 mg

Approved disintegration method at release and stability				Approved disintegration acceptance criterion at release and stability
Source	Apparatus	Medium/ Volume	Temperature	NMT (b) (4)
USP<701>	Basket-Rack assembly with disks	<u>Medium:</u> Water <u>Volume:</u> 1000 mL	<u>Temp:</u> 37 °C	

The proposed drug product is an immediate release product and the baxdrostat API is designated as a BCS class 1 drug substance for the dose strengths of 1 mg and 2 mg and a maximum daily dose of 2 mg. Thus, from a Biopharmaceutics perspective, the initial risk is 'Low'. Although the dissolution method/acceptance criterion adopted by the Applicant differ from the method/acceptance criterion recommended by the *Guidance*, in addition to the dissolution profiles of the two strengths being similar and rapid (>85% drug dissolved at the 15-minute time-point) in the adopted (0.01 N HCl) and *Guidance*-recommended (0.1 N HCl), the Applicant's approach, as summarized below in Table 2, would maintain the risk from a Biopharmaceutics perspective at a 'Low' level, and an additional risk mitigation is not required.

Table 2: Risk Assessment

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Low	- The proposed drug product is an immediate release product and the baxdrostat API is designated as a BCS class 1 drug substance. - A relationship between (b) (4) dissolution and disintegration has been established. - Although the dissolution method/acceptance criterion adopted by the Applicant differ from the method/acceptance criterion recommended by the <i>Guidance</i>, the dissolution profiles of the two strengths are similar and rapid (>85% drug dissolved at the 15-minute time-point) in the adopted (0.01 N HCl) and Guidance-recommended (0.1 N HCl) methods. - The disintegration test/acceptance criterion of 'NMT (b) (4)' at release and through stability would ensure that a rapid (>85%) dissolution of the drug product is achieved in 15-minutes.	Low	- The proposed dissolution method (use of 0.01 N HCl) exhibits limited discriminating ability towards (b) (4). - Establishing an <i>in vitro</i> dissolution acceptance criterion of 'Q = (b) (4)% in 20 minutes' for the stability program would imply that the drug product would also satisfy the acceptance criterion at release and ensure that the quality of the drug product is maintained at release and through stability. - The implemented in-process control (IPC) control limit for (b) (4) (1 mg: (b) (4) and 2 mg: (b) (4) would result in a maximum disintegration time of (b) (4) seconds (i.e. (b) (4) minutes) and a maximum dissolution time of (b) (4) minutes. This would minimize the manufacturing of batches with dissolution times that are slower compared to the target/optimal batches, and ensure that the quality of the drug product is maintained at release and through stability. - The disintegration acceptance criterion would minimize the manufacturing of batches with dissolution times that are slower compared to the target/optimal batches, and ensure that the quality of the drug product is maintained at release and through stability.

• **Product Bridging:**

Bridging of drug product formulations across product development:

The composition of the final To-Be-Marketed (TBM) commercial formulation of the drug product differs from the composition of the drug product used in the Phase 1 and Phase 3 clinical studies. The relative bioavailability of a tablet formulation of Baxdrostat manufactured by (b) (4) was compared to the oral solution in healthy subjects. The oral solution was used to evaluate the absolute bioavailability of baxdrostat in support of the BCS class 1 designation. Bridging of the 5 mg (b) (4) tablets (used in Phase 1 studies) and the 1 mg/2 mg (b) (4) tablets (used in Phase 3 studies) to the 1 mg/2 mg To-Be-Marketed (TBM) tablets manufactured by (b) (4) was conducted in two stages:

- *In vitro* dissolution profile comparison of the 5 mg (b) (4) tablet (used in Phase 1 studies) to the 1 mg/2 mg (b) (4) tablets (used in Phase 3 studies).
- *In vitro* dissolution profile comparison of the 1 mg/2 mg (b) (4) tablets (used in Phase 3 studies) to the 1 mg/2 mg (b) (4) TBM tablets based on a BCS class 1-biowaiver.

Thus, the 1 mg/2 mg (b) (4) TBM tablets are satisfactorily bridged to the 1 mg/2 mg (b) (4) tablets used in the Phase 3 studies and the 5 mg (b) (4) tablet used in the Phase 1 studies, and an additional *in vivo* study is not required.

Bridging of manufacturing sites:

The (b) (4) tablets used in the Phase 3 studies are manufactured at (b) (4). The (b) (4) TBM drug product is manufactured at AstraZeneca AB, Sodertalje, SWEDEN. Based on the information submitted in support of the bridging of formulations, the 1 mg/2 mg (b) (4) TBM tablets were bridged to the 1 mg/2mg Phase 3 (b) (4) tablets via a dissolution profile comparison which exhibited very rapid dissolution (>85% dissolution in 15 minutes) in media across the physiological pH range of 1.2 to 6.8. Thus, the bridging of manufacturing sites is found acceptable.

Bridging of batch sizes:

The batch sizes of the drug products used in the clinical studies are (b) (4) and TBM batch sizes are (b) (4). Based on the information submitted in support of the bridging of formulations, the 1 mg/2 mg (b) (4) TBM tablets were bridged to the 1 mg/2mg Phase 3 (b) (4) tablets via a dissolution profile comparison which exhibited very rapid dissolution (>85% dissolution in 15 minutes) in media across the physiological pH range of 1.2 to 6.8. Thus, the bridging of batches sizes between the clinical and TBM product is found acceptable. The batch sizes of the proposed commercial (b) (4) TBM product range from (b) (4) to (b) (4). The range of the sizes of the proposed commercial (maximum of (b) (4)) and clinical (b) (4) are beyond (b) (4) of each other. From a Biopharmaceutics perspective, the documentation recommended to support the SUPAC-IR level 2 change in batch size would be a multi-point dissolution profile comparison that should be performed in the application/compendial medium. Thus, the bridging of batch sizes is found acceptable.

- **Biowaiver request:**

The Applicant has not requested a biowaiver. Phase 1 studies were conducted on the 5 mg strength of the (b) (4) tablet and Phase 3 studies were conducted on the 1 mg and 2 mg strengths of the (b) (4) tablets. Based on the submitted information, the TBM drug product (1 mg and 2 mg strengths) are satisfactorily bridged to the drug product (1 mg and 2 mg strengths) used in the clinical studies. Thus, a waiver for the (b) (4) TBM drug product is not required.

The list of submissions assessed in the NDA are shown below in Table 3.

Table 3: List of submissions being assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	9/17/2025	Original Submission
NDA	0018	1/12/2026	Response to CMC Information Request
NDA	0021	1/30/2026	Response to CMC Information Request
NDA	0023	2/26/2026	Response to CMC Information Request
NDA	0024	3/13/2026	Response to CMC Information Request

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

None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-219878-ORIG-1 for BAXFENDY™ (Baxdrostat) tablets, 1 mg and 2 mg, is **adequate** and is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Adequate

Solubility:

The active pharmaceutical ingredient (API), baxdrostat, is a crystalline powder. The API has two crystalline solid-state forms that are relevant to the solid dosage form development:

(b) (4). Baxdrostat is a basic compound with a pKa of 5.2. (b) (4)

The solubility of baxdrostat (b) (4) in various media and (b) (4) solvents are shown below in Table 4.

Table 4: Solubility (in buffered solutions) of baxdrostat (b) (4) in various media and (b) (4) solvents

Solvent	Temperature	Solubility at (mg/mL)
pH 1.2	37°C	>80
pH 4.5	37°C	1.1 ^a
pH 6.8	37°C	0.2 ^a
ethanol (99.5%)	20°C	93.0
n-propanol:heptane (45:55 v/v)	20°C	94.0
Heptane	20°C	1.35
methanol	20°C	>94.0

^a

(b) (4)

Permeability:

Baxdrostat is considered to have high permeability according to the BCS criteria with an absolute bioavailability $\geq 85\%$. In addition, the *in vitro* permeability of baxdrostat as assessed in a bi-directional assay in the Caco-2 cell line indicated an apparent permeability higher than that for a high permeability reference compound, minoxidil.

Reviewer's assessment:

The solubility data indicates that the drug substance exhibits a high solubility across the physiological pH range of 1.2–6.8 at 37 °C (80 mg/mL at pH 1.2, 1 mg/mL at pH 4.5, and 0.2 mg/mL at pH 6.8). The highest strength (2 mg) and highest dose (2 mg) are soluble within 250 mL of medium (0.025 mL of pH 1.2 solvent, 2 mL of pH 4.5 solvent, and 10 mL of pH 6.8 solvent). Thus, the baxdrostat API can be considered as a high-solubility drug substance.

A single 3 mg dose of an oral solution compared to a 3 mg dose of an i.v. solution indicates that the absolute bioavailability of baxdrostat at the 3 mg dose is 97.2%. The *in vitro* permeability of baxdrostat in the Caco-2 monolayer model indicates that the $P_{app[A \rightarrow B]}$ for baxdrostat is 19.6×10^{-6} cm/s which is ~2-fold higher than the $P_{app[A \rightarrow B]}$ of the high-

permeability marker, minoxidil (10×10^{-6} cm/s). Thus, baxdrostat can be considered as a high-permeability drug substance.

Based on the high-solubility and high-permeability of the API, in accordance with the May 2021 ICH *Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers*, baxdrostat has been designated as a BCS class 1 compound. The Biopharmaceutics assessment of the BCS Class 1 designation for baxdrostat in IND-146112 is appended below.



I146112 Biopharm
R01.1-AQ.docx

B.2. *IN VITRO* DISSOLUTION METHOD AND ACCEPTANCE CRITERION: Assessment: Adequate

B.2.1. *In vitro* dissolution method:

The August 2018 FDA *Guidance for Industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* establishes standard dissolution methodology and acceptance criteria for drug products that meet the conditions outlined. However, the *in vitro* dissolution method adopted by the Applicant for QC of the drug product for the stability program (as proposed in sequence 0001) differs from the Guidance-recommended method and is shown below in Table 5A:

Table 5A: Proposed *in vitro* dissolution method for QC of the drug product at stability

Apparatus	USP apparatus 1
Medium	0.01 N HCl
Volume	500 mL
Agitation speed	100 rpm
Temperature	37 °C

As part of the dissolution method development, the following dissolution parameters were investigated on the tablets manufactured by the (b) (4) method:

(b) (4)

B.3. CLINICAL RELEVANCE OF DISSOLUTION METHOD AND ACCEPTANCE CRITERION (e.g., IVIVR/IVIVC, *In silico* modeling, small scale *in vivo*):

Assessment: Adequate

Reviewer's assessment:

The Applicant has not performed an IVIVR/IVIVC nor conducted any modeling studies. The proposed drug product is an immediate release product with a mean T_{max} of 2.6 hours and 2.7 hours [study BrighTN (CIN-107-121)] for the 2 mg and 1 mg doses, respectively. The rapid *in vitro* dissolution (>90% of the drug product being dissolved in 20 minutes) is supported by the acceptance criterion of 'Q = (b) (4)% in 20 minutes' and primarily serves as QC of the drug product.

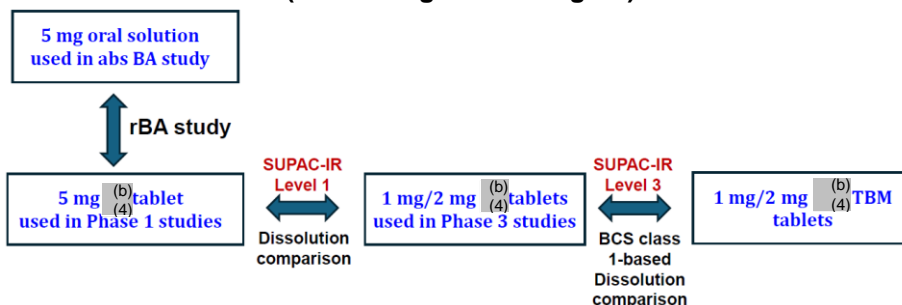
B.12. BRIDGING OF PRODUCTS:

Assessment: Adequate

Bridging of Formulations:

The composition of the final To-Be-Marketed (TBM) commercial formulation of the drug product differs from the composition of the drug product used in the Phase 1 and Phase 3 clinical studies. The relative bioavailability of a tablet formulation of Baxdrostat (manufactured by (b) (4)) was compared to the oral solution in healthy subjects. The oral solution was used to evaluate the absolute bioavailability of baxdrostat in support of the BCS class 1 designation. Additional studies were conducted to bridge the oral solution to the TBM product. Bridging of the 5 mg (b) (4) tablets (used in Phase 1 studies) and the 1 mg/2 mg (b) (4) tablets (used in Phase 3 studies) to the 1 mg/2 mg (b) (4) TBM tablets was conducted in two stages as summarized below in Figure 6.

Figure 6: Bridging of (b) (4) film-coated TBM product to Phase 1/Phase 3 products (Reviewer generated figure)



(i) Bridging of the 5 mg Phase 1 (b) (4) tablet to the 5 mg oral solution:

A randomized, open label, crossover study was conducted to evaluate the relative bioavailability of the tablet formulation of Baxdrostat (CIN-107) as compared to an oral solution and to assess the effect of food on the CIN-107 tablet formulation to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of RO6836191 (Baxdrostat) in healthy male volunteers. The composition of the oral solution is shown below in Table 11A. The composition of the 5 mg tablet used in this Phase 1 studies; manufactured by (b) (4) tablet]) is shown below in Table 11B.

Table 11A: Composition of RO6836191 oral solution, 2 mg/mL (used in absolute BA studies)

Component	Function	Quantity per 100 mL
RO6836191	Drug substance	200 mg
(b) (4)	(b) (4)	(b) (4)

Table 11B: Composition of Baxdrostat 5 mg (b) (4) tablet (used in Phase 1 studies) (Applicant's table)

Components	Quantity per unit (mg)	Quantity (% weight)	Function
Baxdrostat	5.0	(b) (4)	Drug substance
(b) (4)			

The plasma CIN-107 (parent drug) PK parameters by formulation (5 mg oral solution and 5 mg (b) (4) tablet) and food state (fasted and fed) are shown below in Table 11C. The relative bioavailability analysis of the plasma CIN-107 PK parameters following administration of a 5 mg oral (b) (4) tablet (Treatment B) versus a 5 mg dose of oral solution (Treatment A), both in a fasted state is shown below in Table 11D. The food effect on plasma CIN-107 PK parameters following administration of a 5 mg tablet with a standardized high fat meal (Treatment C) versus a 5 mg tablet in a fasted state (Treatment B) is shown in Table 11E.

Table 11C: Plasma CIN-107 (parent drug) PK parameters by formulation (5 mg oral solution and 5 mg (b) (4) tablet) and food state (fasted and fed) (Applicant's table)

PK Parameter (Unit)	Statistic	Treatment A (N=14)	Treatment B (N=14)	Treatment C (N=14)
		n	n	n
C _{max} (ng/mL)	Mean (SD)	53.886 (11.6813)	53.136 (9.7104)	48.593 (9.8807)
	Geom. mean (CV%)	52.727 (21.9)	52.310 (18.6)	47.750 (19.2)
	n	14	14	14
T _{max} (h)	Median (min, max)	2.500 (1.00, 3.50)	3.000 (0.50, 4.07)	4.000 (2.50, 5.00)
	n	14	14	14
AUC _{0-t} (h·ng/mL)	Mean (SD)	1648.853 (371.9217)	1618.128 (384.1689)	1582.033 (378.7624)
	Geom. mean (CV%)	1610.025 (23.1)	1577.696 (23.5)	1542.279 (23.5)
	n	14	14	14
AUC _{0-inf} (h·ng/mL)	Mean (SD)	1752.676 (425.2480)	1721.792 (444.8871)	1690.750 (456.3305)
	Geom. mean (CV%)	1705.336 (24.8)	1671.781 (25.4)	1638.346 (26.1)
	n	14	14	14
AUC _{0-∞} (%)	Mean (SD)	5.565 (2.2131)	5.600 (2.3669)	5.820 (2.9415)
	Geom. mean (CV%)	5.018 (56.4)	4.995 (59.7)	5.109 (60.9)
	n	14	14	14
t _{1/2} (h)	Mean (SD)	28.855 (4.0560)	29.095 (4.7201)	28.984 (5.3055)
	n	14	14	14
λ _z (1/h)	Mean (SD)	0.0246 (0.00411)	0.0245 (0.00451)	0.0247 (0.00459)
	n	14	14	14
CL/F (L/h)	Mean (SD)	3.01 (0.753)	3.08 (0.755)	3.14 (0.773)
	n	14	14	14
V/F (L)	Mean (SD)	122.76 (23.182)	126.10 (25.157)	127.37 (22.145)
	n	14	14	14

A = 5 mg CIN-107 oral solution in a fasted state; B = 5 mg CIN-107 tablet in a fasted state; C = 5 mg CIN-107 tablet in a fed state.

Table 11D: Relative BA of the plasma CIN-107 PK parameters following administration of a 5 mg oral (b) (4) tablet (Treatment B) vs a 5 mg dose of oral solution (Treatment A), both in a fasted state (Applicant's table)

PK Parameter (Unit)	Treatment A		Treatment B		Ratio Geom. LS Mean [1] (B/A) (%)	90% CI for Ratio (%) [2]
	n	Geom. LS Mean [1]	n	Geom. LS Mean [1]		
C _{max} (ng/mL)	14	52.76	14	52.12	98.8	93.10, 104.82
AUC _{0-t} (h·ng/mL)	14	1620.23	14	1584.82	97.8	94.81, 100.91
AUC _{0-inf} (h·ng/mL)	14	1718.54	14	1681.33	97.8	94.71, 101.06

A = 5 mg CIN-107 oral solution in a fasted state; B = 5 mg CIN-107 tablet in a fasted state.

Table 11E: Food effect on plasma CIN-107 PK parameters following administration of a 5 mg (b) (4) tablet with a high fat meal (Treatment C) vs a 5 mg (b) (4) tablet in a fasted state (Treatment B) (Applicant's table)

PK Parameter (Unit)	Treatment B		Treatment C		Ratio Geom. LS Mean (C/B) (%)	90% CI for Ratio (%) [2]
	n	Geom. LS Mean [1]	n	Geom. LS Mean [1]		
C _{max} (ng/mL)	14	52.12	14	47.49	91.1	85.28, 97.36
AUC _{0-t} (h·ng/mL)	14	1584.82	14	1550.17	97.8	94.40, 101.35
AUC _{0-inf} (h·ng/mL)	14	1681.33	14	1648.85	98.1	94.22, 102.07

B = 5 mg CIN-107 tablet in a fasted state; C = 5 mg CIN-107 tablet in a fed state.

Reviewer's assessment:

Based on the 90% CI values for C_{max} , AUC_{0-t} and AUC_{0-inf} being within the acceptance criteria range of 80%–125% (Tables 11D and 11E), this Reviewer concludes that the 5 mg (b) (4) tablet can be considered to be bioequivalent to the 5 mg oral solution under fasting and fed conditions. Assessment of this information is under the purview of the Clinical Pharmacology assessor.

(ii) Bridging of the 5 mg Phase 1 (b) (4) tablet to the 1 mg/2 mg To-Be-Marketed (TBM) (b) (4) tablet:

The 5 mg (b) (4) tablet used in Phase 1 studies was bridged to the 1 mg/2 mg TBM film-coated tablets manufactured by (b) (4) (b) (4) tablets). Bridging was performed in two steps:

- *In vitro* dissolution profile comparison of the 5 mg (b) (4) tablet (used in Phase 1 studies) to the 1 mg/2 mg (b) (4) tablets used in Phase 3 studies.
- *In vitro* dissolution profile comparison of the 1 mg/2 mg (b) (4) tablets (used in Phase 3 studies) to the 1 mg/2 mg (b) (4) TBM tablets.

The composition of the 1 mg/2 mg (b) (4) tablets used in Phase 3 studies and the 1 mg/2 mg (b) (4) TBM tablets are shown below in Tables 11F–11H.

Table 11F: Composition of the 1 mg (b) (4) Phase 3 tablets (Applicant's table)

Components	Quantity per unit (mg)	Quantity (% weight)	Function	Standard*
Baxdrostat	1.0	(b) (4)	Drug substance	AstraZeneca
(b) (4)				

Table 11G: Composition of the 2 mg (b) (4) Phase 3 tablets (Applicant's table)

Components	Quantity per unit (mg)	Quantity (% weight)	Function	Standard*
Baxdrostat	2.0	(b) (4)	Drug substance	AstraZeneca
(b) (4)				

Table 11H: Composition of the 1 mg/2 mg (b) (4) TBM tablets (Applicant's table)

Components	Quantity (% weight)	Quantity per unit (mg)		Function	Standard
		1 mg	2 mg		
Tablet core					
Baxdrostat	(b) (4)	1.0	2.0	Drug substance	AstraZeneca
Lactose anhydrous	(b) (4)				USP/NF
Microcrystalline cellulose	(b) (4)				USP/NF, Ph Eur, JP
Croscarmellose sodium	(b) (4)				USP/NF, Ph Eur
Magnesium stearate	(b) (4)				USP/NF, Ph Eur, JP
Core tablet weight	(b) (4)				NA
Tablet coating					
	(b) (4)	(b) (4)			
	(b) (4) Yellow ^{a, c}	(b) (4)			
Nominal coated tablet weight (mg)	NA	(b) (4)		NA	NA

The mean *in vitro* dissolution profile data for the 5 mg Phase 1 (b) (4) tablet, 1 mg/2 mg Phase 3 (b) (4) tablets and 1 mg/2 mg (b) (4) TBM tablets in 500 mL various buffered media (b) (4) in USP apparatus 1 at 100 rpm, are shown below in Table 11I.

Table 11I: Mean *in vitro* dissolution profile data for the 5 mg Phase 1 (b) (4) tablet, 1 mg/2 mg Phase 3 (b) (4) tablets and 1 mg/2 mg (b) (4) TBM tablets (Reviewer generated table)

Drug Product	pH	% Dissolved (min)					f2 vs 5 mg Ph 1 (b) (4) ab @ pH (b) (4) (Reviewer calculated)
		5	10	15	20	30	
5 mg Ph 1 (b) (4) tablet	(b) (4)	(b) (4)					N.C.
		(b) (4)					N.C.
		(b) (4)					-
1 mg Ph 3 (b) (4) tablet		(b) (4)					N.C.
		(b) (4)					N.C.
		(b) (4)					39.62
2 mg Ph 3 (b) (4) tablet	(b) (4)					N.C.	
	(b) (4)					N.C.	
	(b) (4)					44.85	
1 mg TBM (b) (4) tablet	(b) (4)					N.C.	
	(b) (4)					N.C.	
	(b) (4)					32.54	
2 mg TBM (b) (4) tablet	(b) (4)					N.C.	
	(b) (4)					N.C.	
	(b) (4)					32.75	

N.C.: ≥85% dissolution of both products; thus f2 values were Not Calculated

Reviewer's assessment:

Bridging of 5 mg (b) (4) tablet to the 1 mg/2 mg (b) (4) tablets by *in vitro* dissolution profile comparison:

A comparison of composition of the 1 mg/2 mg Phase 3 (b) (4) tablets (Tables 11F and 11G) to the 5 mg Phase 1 (b) (4) tablets (Table 11B) indicates (b) (4)

(b) (4) between the Phase 1 and Phase 3 products. In accordance with the SUPAC-IR Guidance, this change can be considered as a level 1 change which requires a dissolution documentation in the application/compendial media (Tables 6A and 6B). The dissolution profile data (Table 11I) which demonstrates that the three products

exhibited >85% dissolution in pH (b) (4) and pH (b) (4) media would indicate that the three products would also exhibit >85% dissolution in the agreed upon (application) dissolution media (0.01 N HCl). Thus, the 5 mg Phase 1 (b) (4) tablets can be considered to be effectively bridged to the 1 mg/2 mg Phase 3 (b) (4) tablets.

It is to be noted that at pH (b) (4) the 5 mg Phase 1 (b) (4) tablet exhibits an incomplete dissolution (b) (4) at the (b) (4)-minute time-point which does not support the BCS Class 1 dissolution requirement of baxdrostat for the 5 mg strength. In the IND-146112, the Sponsor attributed the incomplete dissolution of the 5 mg (b) (4) formulation in pH (b) (4) media to a coning effect for the apparatus/rotation speed. This Reviewer notes that the Sponsor does not seek BCS Class 1 designation for the 5 mg strength in the submission, and dissolution profile comparison at pH (b) (4) is not required to bridge the 5 mg (b) (4) tablet to the 1 mg/2 mg (b) (4) tablets.

Bridging of 1 mg/2mg (b) (4) tablets to the 1 mg/2 mg (b) (4) TBM tablets by in vitro dissolution profile comparison:

The 1 mg and 2 mg (b) (4) TBM tablets are compositionally proportional. A comparison of composition of the 1 mg/2 mg Phase 3 (b) (4) tablets (Tables 11F and 11G) to the 1 mg/2 mg (b) (4) TBM tablets (Table 11H) indicates (b) (4). This change (b) (4) can be considered as a level 3 change per the SUPAC-IR Guidance. In addition, the change in the manufacturing process from (b) (4) to (b) (4) can be considered as a level 3 change per the SUPAC-IR Guidance. The level 3 changes require an *in vivo* bioequivalence documentation in addition to the dissolution documentation.

Based on the baxdrostat API being classified as a BCS Class 1 drug substance, the 1 mg/2 mg (b) (4) TBM tablets were bridged to the 1 mg/2mg Phase 3 (b) (4) tablets via a dissolution profile comparison which exhibited very rapid dissolution (>85% dissolution in 15 minutes) in (b) (4).

Based on the totality of the submitted data, this Reviewer concludes that the 1 mg/2 mg (b) (4) TBM tablets can be considered to be satisfactorily bridged to the 1 mg/2 mg (b) (4) tablets used in the Phase 3 studies and the 5 mg (b) (4) tablet used in the Phase 1 studies, and an additional *in vivo* study is not required.

Bridging of Manufacturing sites and batch sizes:

Reviewer's assessment:

The (b) (4) tablets used in the Phase 3 studies are manufactured at (b) (4) (Table 12A). The (b) (4) TBM drug product is manufactured at AstraZeneca AB, Sodertalje, SWEDEN (Tables 12B). The change in the manufacturing site is considered as a level 3 change as per the SUPAC-IR *Guidance*. From a Biopharmaceutics perspective, the documentation recommended to support the level 3 change in manufacturing site is a multi-point dissolution profile comparison that should be performed in the application/compendial medium. Based on the information submitted in support of the bridging of formulations, the 1 mg/2 mg (b) (4) TBM tablets were bridged to the 1 mg/2mg

Phase 3 (b) (4) tablets via a dissolution profile comparison which exhibited very rapid dissolution (>85% dissolution in 15 minutes) in (b) (4) (Table 11I). Thus, the bridging of manufacturing sites is found acceptable.

Table 12A: Details of manufacturing sites and sizes of the clinical batches

Strength and batch number		Batch size (kg)	Batch number of drug substance	Date of manufacture	Site of production	Use
1 mg	L023094	(b) (4)	125403-01	14 December 2022	(b) (4)	Clinical use
2 mg	L023042		125403-01	16 December 2022		Clinical use
2 mg	L024435		128057	16 November 2023		Clinical use
2 mg	L024436		126778	10 January 2024		Clinical use

Table 12B: Details of manufacturing sites and sizes of the TBM batches

Strength and batch number		Batch size (kg)	Batch number of drug substance	Date of manufacture	Site of production	Use
1 mg	EAAB	(b) (4)	24290T0007	27 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability
1 mg	EAAC		24290T0005	28 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability
1 mg	EAAD		24290T0006	28 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability
2 mg	GAAB		24290T0005	12 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability
2 mg	GAAC		24290T0006	13 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability
2 mg	GAAD		24290T0007	13 August 2024	AstraZeneca Sweden Operations, Södertälje	Stability

The batch sizes of the drug products used in the clinical studies are (b) (4) (Table 12A) and TBM batch sizes are (b) (4) (Table 12B). Based on the information submitted in support of the bridging of formulations, the 1 mg/2 mg (b) (4) TBM tablets were bridged to the 1 mg/2mg Phase 3 (b) (4) tablets via a dissolution profile comparison which exhibited very rapid dissolution (>85% dissolution in 15 minutes) in (b) (4) (Table 11I). Thus, the bridging of batch sizes between the clinical and TBM product is found acceptable. The batch sizes of the proposed commercial (b) (4) TBM product range from (b) (4) to (b) (4). The range of the sizes of the proposed commercial (maximum of (b) (4) and clinical (b) (4) are beyond (b) (4) of each other, and is considered as a level 2 change as per the SUPAC-IR *Guidance*. From a Biopharmaceutics perspective, the documentation recommended to support the level 2 change in batch size would be a multi-point dissolution profile comparison that should be

performed in the application/compendial medium. Thus, the bridging of batch sizes is found acceptable.

B.13. BIOWAIVER REQUEST:

Assessment: Adequate

Reviewer's assessment:

The Applicant has not requested a biowaiver. Phase 1 studies were conducted on the 5 mg strength of the (b) (4) tablet and Phase 3 studies were conducted on the 1 mg and 2 mg strengths of the (b) (4) tablets. Based on the submitted information, the TBM drug product (1 mg and 2 mg strengths) are satisfactorily bridged to the drug product (1 mg and 2 mg strengths) used in the clinical studies. Thus, a waiver for the (b) (4) TBM drug product is not required.

R. REGIONAL INFORMATION:

Life Cycle Management Considerations and Risk Mitigation Strategies

Reviewer's assessment:

The proposed drug product is an immediate release product and the baxdrostat API is designated as a BCS class 1 drug substance for the dose strengths of 1 mg and 2 mg and a maximum daily dose of 2 mg. Thus, the risk from a Biopharmaceutics perspective is low. Although the dissolution method/acceptance criterion adopted by the Applicant differ from the method/acceptance criterion recommended by the *Guidance*, in addition to the dissolution profiles of the two strengths being similar and rapid (>85% drug dissolved at the 15-minute time-point) in the adopted (0.01 N HCl) and *Guidance*-recommended (0.1 N HCl), the Applicant's approach, as summarized below, would maintain the risk from a Biopharmaceutics perspective at a low level and additional risk mitigation is not required:

- The dissolution profiles of the drug product in the proposed (0.01 N HCl) and the *Guidance*-recommended media (0.1 N HCl) are similar (>85% of the drug product is dissolved at the 15-minute time-point).
- The proposed dissolution method (use of 0.01 N HCl) exhibits limited discriminating ability towards (b) (4)
- Establishing an acceptance criterion of 'Q = (b) (4)% in 20 minutes' through stability would imply that the drug product would also satisfy the acceptance criterion at release and ensure that the quality of the drug product is maintained at release and through stability.
- The implemented in-process control (IPC) control limit for (b) (4) (1 mg: (b) (4) and 2 mg: (b) (4)) would result in a maximum disintegration time of (b) (4) seconds (i.e., (b) (4) minutes) and a maximum dissolution time of (b) (4) minutes. This would minimize the manufacturing of batches with dissolution times that are slower compared to the target/optimal batches, and ensure that the quality of the drug product is maintained at release and through stability.
- The disintegration test/acceptance criterion of 'NMT (b) (4)' at release and through stability would ensure that a rapid (>85%) dissolution of the product is

achieved in 15-minutes. This would minimize the manufacturing of batches with dissolution times that are slower compared to the target/optimal batches, and ensure that the quality of the drug product is maintained at release and through stability.

BIOPHARMACEUTICS PENDING DEFICIENCIES:

None

13 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

THEODORE E CARVER
05/01/2026 02:42:21 PM