CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216774Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216774, Resub-20
Applicant Name	Teva Pharmaceuticals
Drug Product Name	ALVAIZ (eltrombopag tablets)
Dosage Form.	Tablet
Proposed Strength(s)	9 mg, 18 mg, 36 mg, and 54 mg
Route of Administration	Oral
Maximum Daily Dose	108 mg
Rx/OTC Dispensed	Rx
Proposed Indication	• for the treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. • for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)
Drug Product Description	• 9 mg tablets - Blue, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z9” on the other side • 8 mg tablets - Off-white, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z18” on the other side. • 36 mg tablets - Red, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z36” on the other side. • 54 mg tablets - Orange, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z54” on the other side.

Co-packaged product information	Not Applicable		
Device information:	Not Applicable		
Storage Temperature/ Conditions	Store at 20° to 25°C; excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Akm Khairuzzaman ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5
	Manufacturing	Ke Ren OPMA/DPMAIII/PMB7	Feiyan Jin OPMA/DPMAIII/PMB7
	Biopharmaceutics	N/A	N/A
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
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 (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background:
The Applicant, Teva Pharmaceuticals, submitted this 505(b)(2) NDA for 9 mg, 18 mg, 36 mg, and 54 mg Eltrombopag Tablets, which are intended to be used for the treatment of thrombocytopenia and severe aplastic anemia in specific patient populations. The Applicant seeks approval based on in vivo pharmacokinetic kinetic studies to demonstrate bioequivalence of the proposed drug product to Promacta® (eltrombopag) tablets, which is the listed drug for this application (LD) and the subject of NDA 022291. The previous Integrated Quality Assessment (August 27, 2022) concluded that the NDA was adequate from the OPQ perspective.

2. Drug substance (Eltrombopag choline)*:*
The drug substance is manufactured as the choline salt of eltrombopag, which is a different salt form as compared to the LD, which contains eltrombopag olamine. The NDA cross-references all drug substance CMC information to DMF (b) (4) which remains adequate to support NDA 216774.

3. Drug product (Eltrombopag tablets)*:* No significant revisions to the drug product information were submitted in the NDA resubmission. The drug product review of the NDA resubmission concluded that it remains adequate. Updated stability data (24 months long term stability data) support the proposed shelf life of 24 months. The drug product information remains adequate.

4. Quality labeling*:* The quality aspects of the labeling were previously reviewed and found to be adequate. Minor changes to the quality sections are acceptable. The quality aspects of the labeling remain adequate.

5. Manufacturing:
Process: In Sequence 0020 resubmission, the Applicant proposed minor editorial changes and the removal of a (b) (4) test as an in-process control for (b) (4) which the manufacturing review found to be acceptable.
Facilities: All facilities were found to be compliant as per the previous review. Therefore, the process and facilities for NDA 216774 remain adequate.

6. Biopharmaceutics: No biopharmaceutics review was required because no new biopharmaceutics or manufacturing information requiring review were

submitted, and the NDA remains adequate from the biopharmaceutics perspective.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

See drug product and manufacturing reviews. As indicated in the IQA dated August 27, 2022, manufacturing changes that may affect physicochemical properties of the drug substance or the (b) (4) for the drug product should be supported with appropriate comparative data.

Theodore Carver

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NDA Executive Summary

1. Application/Product Information

NDA Number.	216774
Applicant Name	Teva Pharmaceuticals
Drug Product Name	ALVAIZ (eltrombopag tablets)
Dosage Form.	Tablet
Proposed Strength(s)	9 mg, 18 mg, 36 mg, and 54 mg
Route of Administration	Oral
Maximum Daily Dose	108 mg
Rx/OTC Dispensed	Rx
Proposed Indication	• for the treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. • for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)
Drug Product Description	• 9 mg tablets - Blue, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z9” on the other side • 8 mg tablets - Off-white, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z18” on the other side. • 36 mg tablets - Red, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z36” on the other side. • 54 mg tablets - Orange, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z54” on the other side.

Co-packaged product information	Not Applicable		
Device information:	Not Applicable		
Storage Temperature/ Conditions	Store at 20° to 25°C; excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Akm Khairuzzaman ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5
	Manufacturing	Ke Ren OPMA/DPMAIII/PMB7	Feiyan Jin OPMA/DPMAIII/PMB7
	Biopharmaceutics	Huong Moldthan ONDP/DB/BB3	Kimberly Raines ONDP/DB/BB3
	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
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 (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background:

The Applicant, Teva Pharmaceuticals, submitted this 505(b)(2) NDA for 9 mg, 18 mg, 36 mg, and 54 mg Eltrombopag Tablets, which are intended to be used for the treatment of thrombocytopenia and severe aplastic anemia in specific patient populations. The Applicant seeks approval based on in vivo pharmacokinetic kinetic studies to demonstrate bioequivalence of the proposed drug product to Promacta® (eltrombopag) tablets, which is the listed drug for this application (LD) and the subject of NDA 022291.

2. Drug substance (Eltrombopag choline):

The drug substance is manufactured as the choline salt of eltrombopag, which is a different salt form as compared to the LD, which contains eltrombopag olamine. The NDA cross-references all drug substance CMC information to DMF (b) (4) which was found to be adequate to support NDA 216774. The review assessed starting material design, manufacturing process, characterization, impurities, and physicochemical properties as adequate to support the drug product. The drug substance specification includes appropriate tests and acceptance criteria to support the identity, strength, purity, and quality of the drug substance. Particle size and polymorphic form, critical physicochemical attributes, are also adequately controlled in the drug substance specification.

3. Drug product (Eltrombopag tablets): The drug product was assessed with respect to its critical quality attributes and risks associated with drug product formulation, packaging, specification, and stability. Physicochemical risks to the drug product included changes in particle size and polymorphic form during manufacturing. The drug product composition includes compendial excipients at acceptable levels. In development studies, the Applicant provided data to support stability of the polymorphic form during manufacturing, including evaluation of batches with variations in process parameters such as (b) (4) The drug product specification included acceptable tests and acceptance criteria to assure the identity, strength, purity, and quality of all strengths of the drug product. A stability issue related to tablet discoloration under the accelerated stability condition was identified during review and satisfactorily addressed by the Applicant. The shelf life of 24 months is supported by 12 months of long term and 6 months of accelerated stability data for three stability batches of each strength.

4. Quality labeling: The quality aspects of the labeling were reviewed and found to be adequate after addition of appropriate equivalence statements to comply with requirements for eltrombopag provided as the choline salt.

5. Manufacturing:

Process: (b) (4)

(b) (4)

Facilities: All facilities were found to be acceptable based on previous inspection history.

6. Biopharmaceutics: The biopharmaceutics review focused on the acceptability of the in vitro dissolution test method and acceptance criteria and the biowaiver request for the 9 mg, 18 mg , and 36 mg strengths of eltrombopag. No bridging of formulations used in development was required because no significant manufacturing changes were identified. In response to several information requests, the Applicant provided adequate justification for the final test method parameters and acceptance criteria, as well as data to support the discriminating power of the method with respect to variations in manufacturing. The biopharmaceutics reviewer granted a waiver for the lower strengths based upon the dose proportionality and the dissolution data submitted to the NDA.

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:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

See drug product and manufacturing reviews. Manufacturing changes that may affect physicochemical properties of the drug substance or the (b) (4) (b) (4) for the drug product should be supported with appropriate comparative data.

Theodore Carver

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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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Eltrombopag tablets
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Eltrombopag tablets, 9 mg, 18 mg, 36 mg, and 54 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product
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	Adequate	The strength is based on the active moiety. The API is supplied as a salt in the formulation. Please see further discussion under section 11 later in this review

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	There is no special instruction
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	There is no special administration instruction. This is an immediate release solid oral film coated tablet.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	Not a parenteral dosage form
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	N/A	There is no USP monograph for this product. The API is a new salt of previously approved drug.

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not a radioactive product
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	Not a hazardous product

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablet
Strength(s) in metric system	Adequate	9 mg, 18 mg, 36 mg, and 54 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 (Tablets: 10 mg of drug-x hydrochloride).	Adequate	The strength is based on the active moiety; however the API is 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	The Applicant has provided all the details about identification of the product under section 3.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product

Section 11 (DESCRIPTION) (*SEE NEXT PAGE*)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Eltrombopag tablets
Dosage form(s) and route(s) of administration	Adequate	Tablet, oral
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)”	Adequate	The PI has been corrected as follows: “Eltrombopag tablets contain 9 mg, 18 mg, 36 mg, or 54 mg of eltrombopag (b) (4) 11.10 mg, 22.20 mg, 44.40 mg, and 66.60 mg of eltrombopag choline, respectively.”
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Provided on the label in alphabetical order.
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.	N/A	Not a parenteral product
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol
Sterility statement (if applicable)	N/A	Not a sterile product
Pharmacological/Therapeutic class	Adequate	Thrombopoietin (TPO) receptor agonist
Chemical name, structural formula, molecular weight	Adequate	Provided on label
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive drug
Other important chemical or physical properties (such as pKa or pH)	Adequate	Provided as follows: “Eltrombopag choline is practically insoluble in aqueous buffer across a pH range of 1.2 to 6.8.”

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	N/A	No such statement 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	There is no USP monograph. The API is a new salt of a previously approved drug in the market.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	tablet
Strength(s) in metric system	Adequate	9 mg, 18 mg, 36 mg, and 54 mg
Available units (e.g., bottles of 100 tablets)	Adequate	Bottle of 14 or 180 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Provided
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product
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.”	N/A	None present

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The following statement is provided: "Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	No such statement present
Include information about child-resistant packaging	Adequate	The container closure system use white, ribbed sides, child resistant plastic closure. However, no such description is provided in the labeling. The information is provided under the container/closure system in section 3.2.P.7

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	The following statement has been provided: Manufactured For: Teva Pharmaceuticals Parsippany, NJ 07054 (b) (4) [redacted].

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	Eltrombopag tablets
Special preparation instructions (if applicable)	N/A	None
Storage and handling information (if applicable)	Adequate	The following statements are provided in the medication guide: • Store eltrombopag tablets at room temperature between 68°F to 77°F (20°C to 25°C). • Keep eltrombopag tablets in the bottle given to you.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	product does not contains a desiccant
Active ingredient(s) (if applicable)	Adequate	Provided
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Provided
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	The following statement has been provided: Manufactured For: Teva Pharmaceuticals Parsippany, NJ 07054

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

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

3.1 Container Labels

Reviewer's comment*: Upon sending an IR, the Applicant has revised their container labeling and inserted the equivalence statement as per the FDA's recommendation. A side-by-side labeling comparison has been provided by the applicant as shown above. Accordingly, labeling was changed for all other strengths. This is acceptable now.*

Revised labeling with proposed tradenames (Other strengths follows the same format)

3.2 Carton Labeling

There is no carton

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Eltrombopag tablets (two other trade names are also proposed)
Strength(s) in metric system	Adequate	9 mg, 18 mg, 36 mg, and 54 mg
Route(s) of administration	Adequate	Oral
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Statement has been revised to read as “each tablet contains 9 mg eltrombopag equivalent to 11.10 mg of eltrombopag choline” Similar statement appears on all other strengths.
Net contents (e.g., tablet count, volume of liquid)	Adequate	14 tablets or 180 tablets per bottle
“Rx only” displayed on the principal display	Adequate	Displays “Rx only” statement
NDC	Adequate	Present on container
Lot number and expiration date	Adequate	Present on container
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	Not an injectable product
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not an injectable product
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol
Linear Bar code	Adequate	Present

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	The following statement appears on the container label: “Manufactured For: Teva Pharmaceuticals Parsippany, NJ 07054”
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	There is a medication guide and there is detailed medication guide to each patient on “How should I take eltrombopag tablets?”
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	None

Assessment of Carton and Container Labeling: *{Adequate}*

Equivalence statement has been revised and they are acceptable now.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

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

Overall Assessment and Recommendation: Adequate

The following IR was sent out.

Change the asterisk statement on the container label for the strength to read as "Each tablet contains 9 mg eltrombopag equivalent to 11.10 mg of eltrombopag choline". Similar statement should appear on all other container label for other strengths.

The Applicant has responded on 7/15/2022 and resubmitted all the container closure labeling. The labeling has now included appropriate equivalence statement and they are now acceptable.

Primary Labeling Assessor Name and Date: Akm Khairuzzaman, Ph.D., 7/15/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Theodore Carver, Ph.D. 7/15/2022

Akm Khairuzzaman

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BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	Alvaiz™ (eltrombopag choline) Tablets
NDA Number	216774
Assessment Cycle Number	Original-1
Drug Product Name/ Strength	Eltrombopag Choline Immediate Release Tablets / Eq. to 9 mg, 18 mg, 36 mg, and 54 mg Eltrombopag
Route of Administration	Oral
Sponsor Name	Teva Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DNH
LD Number	NDA-022291 (Promacta® (eltrombopag olamine) Tablets, Novartis Pharmaceuticals Corp.
Proposed Indication	Indicated for the treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Assessment Recommendation: **Adequate**

Assessment Summary:

Teva Pharmaceutical Inc. (The Sponsor) is seeking approval of Alvaiz™ (Eltrombopag Choline Tablets, Eq. to 9 mg, 18 mg, 36 mg, and 54 mg of Eltrombopag), submitted on 12/03/2021 under NDA-216774 via the 505(b)(2) pathway using Promacta® (Eltrombopag Olamine) Tablets as the listed drug (LD). The Sponsor's drug product has the same active moiety, indication, dosage form, dosing regimen and route of administration as the LD. The proposed drug product differs from Novartis Pharmaceuticals' Promacta® (eltrombopag olamine) tablets, for oral use, with respect to the active ingredient salt and strengths.

In support of this application, the Sponsor submitted an *in vivo* bioequivalence study comparing the proposed Eltrombopag Choline Tablets, Eq. to 54 mg of Eltrombopag, to the LD, Promacta® 75 mg, as well as *in vivo* bioavailability studies against Promacta® 25 mg and 50 mg strengths.

The Biopharmaceutics Assessment will focus on the following:

1. Acceptability of in the *in vitro* dissolution test method and acceptance criteria, include discriminatory ability and clinical relevance.
2. Biowaiver for Eltrombopag Choline Tablets, Eq. to 9 mg, 18 mg, and 36 mg, of eltrombopag.

1. Dissolution Method and Acceptance Criteria:

The drug substance (API), Eltrombopag is practically insoluble in aqueous medium across pH 1.2 – pH 6.8 buffer solution. The Sponsor claims Eltrombopag belongs to BCS class 2/4 due to low solubility. (b) (4) An information request (IR) dated 04/07/2022 was sent for justification of the proposed dissolution method. The Sponsor's responses are considered satisfactory (IRs, Responses, and Assessment are detailed under the APPENDIX A "BIOPHARMACEUTICS LIST OF DEFICIENCES"). The proposed quality control dissolution specification (method and criterion) Table 1 is acceptable, as the surfactant concentration was reduced from (b) (4)% to 0.25% while maintaining sink conditions and the agitation speed was adjusted from (b) (4) rpm to 75 rpm minimize variability due to coning during dissolution testing.

Table 1. Dissolution Method and Acceptance Criterion for Eltrombopag Choline

Apparatus	Agitation Speed (rpm)	Dissolution Medium/Temperature	Dissolution Medium Volume (mL)	Dissolution Acceptance Criterion
USP II (Paddle)	75	0.25% Tween 80 in 0.05 M pH 6.8 potassium phosphate buffer, pH 6.8 at 37°C ± 0.5°C	900	NLT (b) (4)% (Q) in 30 min

2. Biowaiver:

In accordance with 21 CFR 320.22(d) / 21 CFR 320.24(b)(6), the Sponsor requested a waiver of evidence of in-vivo bioavailability requirements for Eltrombopag Choline Tablets, Eq. to 9 mg, 18 mg, and 36 mg of Eltrombopag. Acceptability of the biowaiver is based on (1) evaluation of the acceptable in vivo BE on the highest strength (2) formulation proportionality across all strengths and (3) acceptable dissolution for the product line.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0000 (1): original submission **0006 (6): Response to IR #1**	**12/03/2021** **06/02/2022**

Highlight Key Issues from Last Cycle and Their Resolution: Bellow is summary of previous cycle:

IND 139539

Reference is made to your August 24, 2021, submission to IND 139539 regarding the proposed dissolution method for testing of the drug product and the request for Agency feedback.

We acknowledge the submission of the proposed dissolution method (USP II, Compendial Vessel, 75 rpm, 900 mL of 0.25% Tween 80 in 0.05M pH 6.8 potassium phosphate buffer) for quality control of Eltrombopag Choline Tablets for Agency's assessment. The selection of apparatus, agitation speed, medium volume, and medium pH is justified based on the provided dissolution data. However, the decision on the acceptability of the proposed dissolution method could not be made at this stage due to the following:

1. *The selection of surfactant concentration of 0.25% Tween 80 is not completely justified due to the absence of dissolution data generated using* (b) (4)
2. *Complete details on aberrant and target batches representing changes in* (b) (4) *were not provided. Specifically, the target and deviated values of* (b) (4) *were not provided and therefore it could not be concluded if the changes represented meaningful deviations.*
3. *The use of batch manufactured without* (b) (4) *process do not represent meaningful change for discriminating ability of the dissolution method as this deviation is not expected in routine manufacturing. It was stated that* (b) (4) (b) (4) (b) (4)
4. *The levels of* (b) (4) *evaluated for discriminating ability represent* (b) (4) *% change which is not a meaningful deviation.*

We therefore recommend exploring (b) (4) *to evaluate if it provides complete release and lower variability in dissolution. If the data supports* (b) (4)*, we recommend to reconduct studies to demonstrate its discriminating ability towards meaningful changes in critical attributes of the drug product.*

Consider the above comments regarding target and aberrant batches for discriminating ability studies. Also, note that discriminating ability of the dissolution method should be demonstrated by both the dissolution profile similarity test and the proposed dissolution acceptance criterion. Specifically, aberrant batches should be rejected by profile similarity ($f2 < 50$) and proposed dissolution acceptance criterion. Pending the acceptability of the dissolution method, we recommend testing batches that are used in any ongoing pivotal clinical/PK study with both methods (b) (4) *Address the above recommendations in an IND amendment seeking acceptability of*

the quality control dissolution method. Alternatively, submit the dissolution method development report in NDA submission addressing the above recommendations.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: The submission does not contain a request for BCS Designation.

Solubility: The active ingredient (API), Eltrombopag Choline is practically insoluble in aqueous medium across at pH 1.2; 4.5 and 6.8 buffer solution. The Sponsor states that the API is BCS class 2/4.

Table 2. Solubility of Eltrombopag and Eltrombopag Choline

pH	Buffer Solution	Solubility (mg/mL)	
		Eltrombopag	Eltrombopag Choline
1.1	0.1 N HCl	0.0000	0.0000
1.1	0.1% Tween 80 in 0.1 N HCl	0.0025	0.0031
1.1	0.25% Tween 80 in 0.1 N HCl	0.0066	0.0081
1.1	0.5% Tween 80 in 0.1 N HCl	0.0122	0.0150
1.1	0.75% Tween 80 in 0.1N HCl	0.0204	0.0252
1.1	1% Tween 80 in 0.1N HCl	0.0245	0.0302
4.5	pH 4.5	0.0025	0.0031
4.5	0.1% Tween 80 in pH 4.5 acetate buffer	0.0060	0.0074
4.5	0.25% Tween 80 in pH 4.5 acetate buffer	0.0099	0.0122
4.5	0.5% Tween 80 in pH 4.5 acetate buffer	0.0212	0.0261
6.8	pH 6.8	0.0130	0.0160
6.8	0.1% Tween 80 in pH 6.8 phosphate buffer	0.0847	0.1045
6.8	0.25% Tween 80 in pH 6.8 phosphate buffer	0.1791	0.2209
6.8	0.5% Tween 80 in pH 6.8 phosphate buffer	0.3011	0.3713

Conditions: Room Temperature

Permeability: Not provided.

Dissolution: Under tested conditions dissolution where solubility achieved (Table 2) in vitro dissolution is very rapid (> (b) (4)% release in (b) (4) minutes) for all strengths of the Eltrombopag Choline Tablets.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

The Sponsor claims Eltrombopag belongs to BCS class 2/4 due to low solubility. (b) (4) The Sponsor develops their in-house dissolution method (Table 1) (b) (4)

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Table 4. Individual dissolution data of biobatch Lot 241356R04, Eq. 54 mg Eltrombopag Choline using proposed dissolution method

Lot 241356R04 /Paddle, 75 rpm, 900 mL; Time (Minutes)/Eltrombopag Choline 54mg Tablets dissolution-Media: 0.25% Tween 80 in SIF (pH6.8 Potassium Phosphate Buffer)						
No of Units	**5**	**10**	**15**	**20**	**30**	**45**
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

*Reporting error

Table 5. Proposed dissolution method and acceptance criterion for quality control of Eltrombopag Choline Tablets, Eq. to 9 mg, 18 mg, 36 mg, and 54 mg of Eltrombopag

Dissolution Conditions	Apparatus	USP II (paddle)
	Speed of Rotation	75 rpm
	Medium	0.25% Tween 80 in 0.05M pH 6.8 potassium phosphate buffer
	Volume	900 mL
	Temperature	37°C ± 0.5°C
Proposed Acceptance Criterion	NLT (b) (4) % (Q) in 30 minutes	

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

Assessment: ***{NA}***

The Sponsor proposed dissolution method and demonstrating its discriminating ability which is acceptable. The proposed acceptance criterion is satisfied as well. The Sponsor did not submit other clinical relevance of dissolution method and acceptance criterion.

Risk Assessment - Eltrombopag Choline exhibits low to no solubility across the physiological pH range. Drug substance solubility strongly impacts dissolution. The risk is high. (b) (4) Therefore, the formulation and drug product manufacturing process are designed to mitigate this risk and dissolution is not rate limiting for the drug product formulation and impact on clinical performance is not greatly influenced.

B.4 BRIDGING OF FORMULATIONS

Assessment: ***{NA}***

Per Drug Product Assessor review, there is no change in composition formulation of the BE batch and clinical batches and therefore no bridging of formulations is not needed for the biopharmaceutics assessment.

B.5 BIOWAIVER

Assessment: From Biopharmaceutics perspective, the waiver request for lower strengths is granted.

Outcome of the BE Study: Per Clinical Pharmacology Reviewer (communicated via email), the in vivo BE study conducting between Eq. 54mg Eltrombopag Choline and 75 mg LD, Promacta is acceptable (as of 8/25/2022).

Formulation Proportionality:

Teva's proposed test product manufactured using the Eltrombopag Choline salt and the (b) (4) resulted in a (b) (4)% dose reduction when compared to the reference product PROMACTA® (eltrombopag) Tablets. The dosage strength 25 mg and 50 mg were used in the comparative bioavailability study (Protocol No.: ACT-19024). Based on the bio-study results the dosage strength is reduced to of 9 mg, 18 mg, 36 mg, 54 mg, and (b) (4) mg. The qualitative and quantitative composition of Teva's proposed product Eltrombopag Choline Tablets and the equivalent strength in PROMACTA® (eltrombopag) Tablets is shown in Table 6. The core tablet formulation of the proposed dosage strengths 9 mg, 18 mg, 36 mg, 54 mg, and (b) (4) mg are dose proportional formulations to the 25 and 50 mg strength.

Table 6: Composition of Drug Product and Function of Components for the Teva's proposed product Eltrombopag Choline Tablets

				Dosage Strength[1]	9 mg	18 mg	36 mg	54 mg
#	Ingredient	% / Core Tablet	Function		mg/Tablet	mg/Tablet	mg/Tablet	mg/Tablet
	Core Tablet							
1	Eltrombopag Choline	13.12	Active		11.10	22.20	44.40	66.60
2	Poloxamer 188 NF (b) (4) Poloxamer 188 NF (b) (4)	(b) (4)						
3	Copovidone, NF (b) (4) (b) (4)							
4	Polyethylene Glycol 4000, (b) (4)							
5	Povidone, NF (b) (4)							
6	Edetate Disodium Dihydrate, USP							
7	(b) (4) Microcrystalline Cellulose (b) (4) (b) (4) (b) (4)							
8	Anhydrous Lactose NF, (b) (4)							
9	Croscarmellose Sodium, NF							
10	Magnesium Stearate, NF							
11	Silicon Dioxide, (b) (4) (b) (4)							
	Core Tablet Weight							

Per Clinical Pharmacology Review of the LD (NDA 022291), the pharmacokinetic parameter [e.g., AUC(0-T) and Cmax] increased in a dose proportional manner between 50 mg and 200 mg and 50 mg and 150 mg, respectively. The current NDA submission, the doses are (b) (4)% reduction from the LD. Therefore, the lowest strength (Eq.9 mg of Eltrombopag) is proportional to the higher strengths (e.g., Eq.18 mg, 36 mg, and 54 mg of Eltrombopag), and all four strengths have pharmacokinetic linear relationship.

Dissolution:

Additionally, the Sponsor submitted the in vitro dissolution profile of the highest strength of 54 mg which is comparable to the other strengths of 9 mg, 18 mg, and 36 mg. Based on the submitted data, the means of dissolution data of all strengths are more than (b) (4)% of Eltrombopag dissolved in (b) (4) minutes, therefore, the f2 calculation if not required. However, due to the high variability at (b) (4) and (b) (4) minutes of the highest strength of 54 mg, the Booth Strapping approach (Automation Tool of Division of Biopharmaceutics) was used to calculate f2 and the f2 value is higher than 50. The detail of analysis is presented in Figure 5, Figure 6, Figure 7, and Table 7.

Table 7. Summary of Bootstrapping results of comparison dissolution of Strengths, Eq. 9 mg, 18 mg, and 36 mg to Strength of Eq 54 mg of Eltrombopag

In bootstrapping, the similarity can be verified if the lower bound of the confidence interval is larger or equal to 50

MEAN	0	5	10	15	20	30	45
Test.18.mg	(b) (4)						
Test.36.mg							
Test.54.mg							
Test.9.mg							

Therefore, from Biopharmaceutics perspective, the waiver of lower strengths is granted.

Figure 5. Comparative Dissolution Profiles of the Lowest Strength to the Highest Strength, Eq. 9 mg and Eq 54 mg of Eltrombopag, respectively.

Figure 6. Comparative Dissolution Profiles of the Strengths of Eq. 18 mg and Eq 54 mg of Eltrombopag, respectively.

Figure 7. Comparative Dissolution Profiles of the Strengths of Eq. 36 mg and Eq 54 mg of Eltrombopag, respectively.

Overall Assessment Summary:

The proposed dissolution method [USP II (Paddles), 900 mL of 0.25% Tween 80 in 0.05M pH 6.8 potassium phosphate buffer for at 75 rpm, 37°C ± 0.5°C] and acceptance criterion of NLT (b) (4)% (Q) in 30 minutes for quality control of the proposed drug product, Alvaiz™ (Eltrombopag Choline Tablets / Eq. to 9 mg, 18 mg, 36 mg, and 54 mg) are acceptable. The waiver of lower strengths is granted. From a Biopharmaceutics perspective, the proposed NDA 216774 is recommended for approval.

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