CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216774Orig1s000

SUMMARY REVIEW

Date	(electronic stamp)
From	Margaret Thompson MD
Subject	CDTL Memo
NDA/BLA # and Supplement #	NDA 216774
Applicant	Teva Pharmaceuticals, Inc (Teva)
Date of Submission	9/29/2023
Proprietary Name	ALVAIZ
Established or Proper Name	Eltrombopag choline
Dosage Form(s) / Strength	tablets of strengths 9 mg, 18 mg, 36 mg, and 54 mg
Route of Administration	oral
Indication(s)/Population(s)	1) for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. 2) for the treatment of thrombocytopenia in adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. 3) for the treatment of adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
Proposed Dosage	Initial Dose Regimen: Adult and Pediatric Patients 6 Years and Older with ITP: Initiate ALVAIZ at a dose of 36 mg orally once daily, except in patients who are of East-/Southeast-Asian ancestry or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C). For patients of East-/Southeast-Asian ancestry with ITP, initiate ALVAIZ at a reduced dose of 18 mg once daily. For patients with ITP and mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate ALVAIZ at a reduced dose of 18 mg once daily. For patients of East-/Southeast-Asian ancestry with ITP and hepatic impairment (Child-Pugh Class A, B, C), consider initiating ALVAIZ at a reduced dose of 9 mg once daily. After initiating ALVAIZ, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 109 /L as necessary to reduce the risk for bleeding. Do not exceed a dose of 54 mg daily.
Regulatory Pathway	505(b)(2)
Action:	Approve
Approved Dosage	Same as proposed dosage

1) **Recommendation: The Division recommends regular approval for ALVAIZ (eltrombopag choline) tablets of strengths 9 mg, 18 mg, 36 mg, and 54 mg under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the requested indications.**

2) **Background**

a) On December 3, 2021, Teva submitted a New Drug Application (NDA 216774) for ALVAIZ (eltrombopag choline) tablets of strengths 9 mg, 18 mg, 36 mg, and 54 mg under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Eltrombopag choline is a new salt form of eltrombopag. The application relied on Agency's safety and efficacy findings for the listed drug (LD) PROMACTA® (eltrombopag olamine) tablets approved under NDA 022291 in 2008. No additional clinical efficacy or safety data was presented in this application and no new claims were sought.

b) On October 3, 2022, the Agency granted tentative approval given that the ODE-210 exclusivity which is indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia had not expired.

c) On September 29, 2023, Teva resubmitted their NDA 216774 for ALVAIZ (eltrombopag tablets) in response to the tentative approval previously granted. Teva requested final approval for ALVAIZ for the following indications:

- for the treatment of thrombocytopenia in adult and pediatric patients 6 years 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 adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- for the treatment of adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

3) **Regulatory: The Applicant provided the following rationale and supporting documents in support of regular approval:**

a) The Listed Drug Promacta® (eltrombopag) tablets, for oral use (NDA 022291), was approved by FDA on November 20, 2008.

b) Teva's NDA No. 216774 received a "Date (Received) Acceptable for Review" of December 3, 2021.

c) The application included a Paragraph IV Certification for U.S. Pat. Nos. 7,547,719; 7,795,293; 8,052,993; 8,052,994; 8,062,665; 8,071,129; and 8,828,430, pursuant to 21 USC §355(b)(2)(A)(iv) and 21 CFR §314.50(i)(1)(i)(A)(4)(i), stating that the patents were invalid, unenforceable, or would not be infringed by the manufacture, use or sale of Teva's Eltrombopag Choline Tablets (NDA # 216774).

d) A PIV Certification for the '719, '293, '993, '994, '665, '129 and '430 patents was submitted on December 3, 2021 with the filing of the original NDA.

e) A revised Patent Certification was submitted with the original NDA, which included method-of-use codes for the '993, '994, '665, and '129 patents. Additionally, the revised Patent Certification included a Section viii certification for the '719 patent with the U-2452 Use Code, specifically a statement pursuant to 21 CFR §314.94(a)(12)(iii)(A) for U.S. Pat. No. 7,547,719, that pursuant to

Section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act, the labeling of the drug product for which Teva is seeking approval under this NDA does not include information that is covered by the Use Code U-2452 of said patent.

f) The application included a Paragraph III Certification for U.S. Pat. No. 7,160,870, pursuant to 21 USC §355(b)(2)(A)(iii) and 21 CFR §314.50(i)(1)(i)(A)(3).
- A PIII Certification for the '870 patent with PED was submitted on December 3, 2021 with the filing of the Original NDA . Teva noted that Patent 7,160,870*PED expired on May 20, 2023.
- Teva notified the Agency on May 13, 2022 that no lawsuits were filed with respect to the U.S. Patent Nos. 7,547,719, 7,795,293, 8,052,993, 8,052,994, 8,062,665, 8,071,129, and 8,828,430 within the 45 days' notice. Notice was received by Novartis Pharmaceutical on February 9, 2022 (East Hanover, NJ) and February 10, 2022 (Switzerland).
- In compliance with the Pediatric Research Equity Act (PREA), Teva committed to the Agency on September 23, 2022 as a Postmarketing Requirement (PMR) to develop an appropriate formulation for Alvaiz (eltrombopag choline) that can be used to directly and accurately administer Alvaiz (eltrombopag choline) to pediatric patients less than 6 years of age, and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure and administer the appropriate doses.
- Teva provided the Agency on December 21, 2022, a copy of the letter dated December 7, 2022, which was submitted to the FDA by the law firm of (b) (4) regarding the Orphan Drug Exclusivity After Catalyst.

4) Labeling

a) Labeling was revised by the Applicant in accordance with the labeling for the LD Promacta (most recently approved 7/6/2023 (S-37)).

b) Labeling was reviewed and approved with minor editorial revisions.

5) Chemistry, Manufacturing, and Controls Information

a) The resubmission included the following CMC information: manufacturer and corrected (b) (4) Coating (b) (4) information. The Applicant noted that the drug substance specifications, drug substance test method, finished product specifications and test methods have not changed.

6) Post Marketing Requirement (PMR)/ Post Marketing Commitment (PMC)

The following PMR was issued with the approval:

4554-1 Develop an appropriate formulation for Alvaiz (eltrombopag choline) that can be used to directly and accurately administer Alvaiz (eltrombopag choline) to pediatric patients less than 6 years of age. Conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure and administer the appropriate doses.

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/s/

MARGARET C THOMPSON
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Cross-Discipline Team Leader Memo

Date	(electronic stamp)
From	Margaret Thompson MD
Subject	CDTL Memo
NDA/BLA # and Supplement #	NDA 216774
Applicant	Teva Pharmaceuticals, Inc
Date of Submission	12/3/2021
PDUFA Goal Date	10/3/2022
Proposed Proprietary Name	Alvaiz
Established or Proper Name	eltrombopag choline
Dosage Form(s) / Strength	Tablets Equivalent to 9 mg, 18 mg, 36 mg, and 54 mg
Route of Administration	Oral
Applicant Proposed Indication(s)/Population(s)	• 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. ALVAIZ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. • for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. ALVAIZ should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. • for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
Regulatory Pathway	505(b)(2)
Licensed Drug (LD)	Promacta®(eltrombopag) tablets, (NDA 022291)
Action:	Tentative Approval*
Approved Indication(s)/Population(s) (if applicable)	• for the treatment of thrombocytopenia in adult and pediatric patients *6 years and older* with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. ALVAIZ should be used only in patients with ITP whose degree of

	thrombocytopenia and clinical condition increase the risk for bleeding. • for the treatment of thrombocytopenia in adult patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. ALVAIZ should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. • for the treatment of adult patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

* final approval delayed until all exclusivity issues have been resolved.

Reviews

Discipline/ Office	Primary Reviewer/Secondary Reviewer
Clinical	Patricia Oneal/ Margaret Thompson
Clinical Pharmacology	Hebing Liu/ Sudharshan Hariharan
OPQ Drug Substance	Ben Zhang/ Zhengfu Wang
OPQ Drug Product/ Labeling	Akm Khairuzzaman/ Theodore Carver
OPQ Manufacturing	Ke Ren/ Feiyan Jin
OPQ Biopharmaceutics	Huong Moldthan/ Kimberly Raines
Division Labeling	Virginia Kwitkowski

Consults

Office	Consultant
OPDP	Melissa Khashei
DMPP	Sharon Mills
OSE/DMEPA	Hina Mehta

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction

Teva Pharmaceuticals submitted NDA 216774 for eltrombopag choline (Alvaiz, original proposed name) 9 mg, 18 mg, 36 mg, and 54 mg tablet strengths in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. GlaxoSmithKline's eltrombopag olamine (PROMACTA®) was approved by the Food and Drug Administration (FDA) on November 20, 2008 (NDA 022291). Eltrombopag is the active moiety. The Teva Pharmaceutical product's drug substance is manufactured as the choline salt of eltrombopag, which is a different salt form as compared to the listed drug (LD), which contains eltrombopag olamine. The proposed drug, eltrombopag choline, has the same active moiety, dosage form, dosing regimen, and route of administration as the LD. Eltrombopag choline differs from the LD with respect to the active ingredient salt and strengths. The application relies on Agency's safety and efficacy findings for the LD. No new claims are being sought with this application.

PROMACTA® is approved for the four following indications:

1) for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of

thrombocytopenia and clinical condition increase the risk for bleeding. (1.1)

2) for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon- based therapy or limits the ability to maintain interferon-based therapy.
3) in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
4) for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Teva is seeking the following indications for eltrombopag choline:

1) Thrombocytopenia in adults 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.
2) Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
3) Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

2. Background

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin (TPO)-receptor agonist that interacts the transmembrane domain of the human TPO-receptor and initiates signally cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag olamine is approved for the treatment of thrombocytopenia and severe aplastic anemia in specific patient populations.

3. Product Quality

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities reviewers) recommends APPROVAL for NDA 216776.

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 OPQ review assessed starting material design, manufacturing process, characterization, impurities, and physicochemical properties as adequate to support the drug product. The drug substance specification included 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.

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. 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. In the course of the OPQ review, 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.

Manufacturing

(b) (4)

(b) (4) All facilities were found to be acceptable based on previous inspection history.

Biopharmaceutics

No bridging of formulations used in development was required because no significant manufacturing changes were identified.

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. In response to 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.

4. Clinical Pharmacology:

Overall Clinical Pharmacology Recommendation: The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) recommends APPROVAL for NDA 216776.

The Applicant conducted two pharmacology studies, a bioavailability (BA) study and a bioequivalence study (BE).

1) Study ACT-19024 is an open label, randomized, 4-way crossover study to assess the comparative bioavailability of eltrombopag choline tablets, 25 mg and 50 mg to PROMACTA® tablets, 50 mg under fasted conditions, as well as the food effect of the Applicant's formulation.

2) Study # ACT-21003 is an open-label, randomized, single dose, two-way crossover bioequivalence study comparing eltrombopag choline tablets, 54 mg to PROMACTA® (eltrombopag) tablets, 75 mg under fasted conditions.

Office of Study Integrity and Surveillance (OSIS) determined that inspection of the clinical and bioanalytical sites for the pivotal relative BA study (ACT-21003) were not warranted at this time, as the sites were recently inspected and were classified as No Action Indicated (NAI).

Summary of clinical pharmacology findings:

- The results of the relative BA study (ACT-19024) demonstrate that eltrombopag choline tablets, 25 mg or 50 mg and the listed drug, PROMACTA® (50 mg tablet), are not bioequivalent. ALVAIZ 25 mg has 29% lower Cmax and AUC_0-t compared to PROMACTA® 50 mg. ALVAIZ 50 mg has 32% higher Cmax and 34% higher AUC_0-t compared to PROMACTA® 50 mg. These results indicated that ALVAIZ has a higher bioavailability compared to PROMACTA® and only a strength that is approximately 30% lower will likely be equivalent to the corresponding strength of PROMACTA®.

- The results of the pivotal relative BA study (ACT-21003) demonstrate that eltrombopag choline tablets 54 mg and the listed drug, PROMACTA® (75 mg tablet), are bioequivalent under fasted conditions.

- Administration of eltrombopag choline after a high fat, high calorie meal decreased AUC_{inf} by approximately 36% and Cmax by approximately 39% as compared to fasted conditions in Study ACT-19024.

- The bioanalytical method used to measure eltrombopag choline is validated and the performance of the method in the clinical studies is acceptable as per the specifications outlined in the Bioanalytical Method Validation Guidance.

5. Clinical

Overall clinical recommendation: The Office of Cardiology, Hematology, Endocrinology, and Nephrology/ Division of Non-Malignant Hematology (OCHEN/DNH) recommends APPROVAL for NDA 216776.

The only clinical studies were the comparative BA and BE studies discussed above with clinical pharmacology findings. The Applicant relied on safety and effectiveness data from the LD. As part of the clinical review, a literature search was performed to assess whether the currently labeling was sufficient to provide adequate instructions for use. No new safety issues were identified.

6. **Labeling**

The labeling was submitted in PLR and PLLR format. Other eltrombopag olamine labeling, comprising NDA 022291 (the LD), NDA 209027 (powder and suspension formulations of the LD), and 9 ANDAs, were reviewed as part of the clinical and labeling review process.

Key changes to the proposed labeling:

- The indication statement for the treatment of thrombocytopenia in adult and pediatric was restricted to patients 6 years and older to reflect a population capable of swallowing tablets.
- The indication statement for the treatment of aplastic anemia was restricted to treatment of adult patients consistent with the Indications and Usage guidance regarding inclusion of population age.

- Addition of subsection 2.1 due to different tablet strengths between ALVAIZ and other eltrombopag products, including a statement that ALVAIZ is not substitutable with other eltrombopag products on a milligram per milligram basis.
- Addition of linkage statement because of the different salt form from reference drug in Section 6.1 and Section 14.
- Deletion of aplastic anemia indication in Section 8.4 as it is protected by exclusivity.
- Addition of statement indication safety and effectiveness of ALVAIS not established in patients < 6 years of age with persistent of chronic ITP to Section 8.4.

7. Postmarketing requirements (PMR)

Based on recommendations of the Division of Pediatric and Maternal Health (DPMH), the following PREA postmarketing requirement (PMR) will be submitted to the Applicant at the time of final approval.

- Develop an appropriate formulation for Alvaiz (eltrombopag choline) that can be used to directly and accurately administer Alvaiz (eltrombopag choline) to pediatric patients less than 6 years of age. Conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure and administer the appropriate doses.

8. Exclusivities

Review of Orange Book identified the following exclusivities:

- Associated with NDA 022291 (25, 50, 75 mg tablets of the LD) are ODE-75*PEDS (expired 02/26/2022) and ODE-210 (expires 11/16/2025)
    - ODE-210 is for the following indication: indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
- Associated with NDA 207027 (12.5 and (b) (4) mg powder and suspension formulations of the LD) are ODE-74*PEDS,ODE-PEDS (expired 02/26/2022), and ODE-210.
    - ODE-210 is for the following indication: indicated in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.

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/

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