Clinical Review of 505(b)(2) Application

Submission Date	December 3, 2021
NDA#	216774
SD#	1
Drug Name: Non-Proprietary (Proprietary, if appl.)	Eltrombopag Choline (Alvaiz®) 9 mg, 18 mg, 36 mg, and 54 mg tablets
Indication(s) Sought	• 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. Eltrombopag tablets 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. Eltrombopag tablets 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. Limitations of Use: • Eltrombopag tablets are not indicated for the treatment of patients with myelodysplastic syndrome (MDS). • Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.
Clinical Reviewer	Patricia Oneal, MD
Clinical Team Leader	Margaret Thompson, MD, PhD

Actions Recommended: Tentative Approval

Reference ID: 5052340

Executive Summary

Teva Pharmaceuticals, Inc has 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. The application relies on Agency's safety and efficacy findings for the listed drug 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 are being sought with this application.

The clinical review included the following:

- A literature search to identify potential new safety information to determine whether current labeling was sufficient to provide adequate instructions for use. No new safety information not already adequately labeled was identified.
- A review of other eltrombopag labelings (NDAs and ANDAs). No safety information not included in the proposed labeling for eltrombopag choline was identified.
- Review of Orange Book for outstanding exclusivities for eltrombopag, identifying one outstanding exclusivity – ODE-210, which expires November 16, 2025.

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

Background of Application:

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Teva Pharmaceuticals, Inc has submitted NDA 216774 for Eltrombopag choline (Alvaiz®) 9 mg, 18 mg, 36 mg, and 54 mg tablets. Eltrombopag choline is a new salt form of eltrombopag. The active moiety Eltrombopag olamine (Promacta®) was approved by the Food and Drug Administration (FDA) on November 20, 2008 (NDA 022291) which is held by GlaxoSmithKline. Teva Pharmaceuticals is relying on the previously established safety and efficacy data of the reference listed drug (RLD) product, NDA 022291 for Eltrombopag olamine 12.5 mg, 25 mg, 50 mg, and 75 mg tablets.

Documents Reviewed:

SD-1 (December 3, 2021)

Module 1

- Forms
- Cover Letter
- Administrative Information
    - Financial Certification and Disclosure
    - Patent and Exclusivity
- Correspondence regarding Meetings
- Proposed Pediatric Study Request and Amendments
- Labeling (draft, annotated and Listed Drug Labeling)

Reference ID: 5052340

Module 5

- Clinical Study Reports
- Comparative BA and Bioequivalence (BE) Study Reports
    - ACT-19024: Open label, randomized, single dose, four-way crossover comparative bioavailability study of Eltrombopag, 25 mg and 50 mg in healthy human, adult males and females of non-childbearing potential under fasting and fed conditions
    - ACT-21003: Open label, randomized, single dose, two-way crossover bioequivalence study of Eltrombopag Choline Tablets, 54 mg Eltrombopag in healthy human, adult males and females of non-childbearing potential under fasting conditions

Literature Review: A literature review for new safety information regarding eltrombopag was conducted to determine whether the current labeling was sufficient to provide adequate instructions for use. The application does not rely on published literature. The applicant is using the safety and effectiveness data from the listed drug, Promacta® (eltrombopag) tablets.

Review of other Eltrombopag Labelings:
There are 2 actively marketed NDAs for Eltrombopag olamine. Their numbers are 22291 (the RLD) and 207027 (powder and suspension of the RLD). There are (4) ANDAs for eltrombopag olamine ((b) (4)

Summary of Review Findings:

This reviewer conducted a PubMed database search for recent publications regarding eltrombopag safety, and no new issues were identified.

Orange Book Status/Outstanding Exclusivities for Approved NDAs:

NDA#	Outstanding Exclusivities	Outstanding Patents
22291 (RLD)	ODE-75*PED: Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy; exclusivity expired on 02/26/2022 ODE-210: 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. Exclusivity expires on 11/16/2025.	There are no unexpired patents for this product in the Orange Book database. Patent #7160870 expires on 11/20/2022 (Use codes U-1306 and U-1736)
207027 (RLD for powder and suspension)	ODE-74*PED and ODE-PED: The exclusivity has expired on 02/26/2022.	There are no unexpired patents for this product in the Orange Book database.

Reference ID: 5052340

		Patent #7160870 expires on 11/20/2022 (Use codes U-1306 and U-1736)
ELTROMBOPAG OLAMINE EQ 100MG ACID **Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons**		

The Division and DPMH concur that the indications tied to ODE-75 and ODE-75*PEDS are distinct from the indication linked to ODE-210. There is no need for the disclaimer since the indication is not being sought out by the Applicant.

Labeling:

The labeling was submitted in PLR and PLLR format. We have had five multidisciplinary labeling meetings held on June 8, 2022, June 22, 2022, July 12, 2022, July 20, 2022, August 23, 2022, September 13, 2022.

PeRC meeting is scheduled for August 9, 2022. PeRC recommendation is to request for a postmarketing requirement (PMR) for the Applicant to develop an appropriate formulation for Alvaiz® (eltrombopag choline) that can be used to administer Alvaiz® (eltrombopag choline) directly and accurately to pediatric patients less than 6 years of age. The Sponsor should also conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure and administer the appropriate doses

In labeling discussions, we have recommended revisions based upon guidances published since the approval of the last version and revisions of the RLD labeling of previously approved eltrombopag products. For details regarding the rationale for specific proposed labeling changes, refer to the Labeling Review by Virginia Kwitkowski archived on 26 September 2022.

Regulatory Conclusion:

NDA 216774 is recommended for tentative approval from the clinical and DPMH perspective 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 has not expired (expires on 11/16/2025).

The clinical PMR for this eltrombopag choline application will be submitted to the Applicant upon final approval.

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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