CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216774Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 28, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216774
Product Name, Dosage Form, and Strength:	Alvaiz (eltrombopag) tablets, 9 mg, 18 mg, 36 mg, and 54 mg
Applicant/Sponsor Name:	Teva Pharmaceuticals Inc. (Teva)
TTT ID #:	2023-6764-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on November 22, 2023 for Alvaiz. We reviewed the revised container labels for Alvaiz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note the format of the expiration date is YYYY-MM in numerical values. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Black, S. Label and Labeling Review for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 NOV 27. TTT ID No.: 2023-6764.

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

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 22, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216774
Product Name, Dosage Form, and Strength:	Alvaiz (eltrombopag) tablets, 9 mg, 18 mg, 36 mg, and 54 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Teva Pharmaceuticals Inc. (Teva)
FDA Received Date:	September 29, 2023
TTT ID #:	2023-6764
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) class I resubmission for Alvaiz (eltrombopag) tablets, we reviewed the proposed Alvaiz prescribing information (PI), medication guide (MG) and container labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 216774 relies upon the listed drug Promacta tablets, which was approved under NDA 022291 on November 20, 2008. Promacta (eltrombopag) is currently marketed as 12.5 mg, 25 mg, 50 mg, and 75 mg tablets under NDA 022291 and as 12.5 mg and 25 mg for oral suspension packets under NDA 207027.

Teva Pharmaceuticals Inc. (Teva) initially submitted NDA 216774 on December 3, 2021. We reviewed the prescribing information (PI), medication guide (MG) and container labels and determined that the proposed container labels and PI can be improved and we provided recommendations to Division and Teva.[a] On October 3, 2022, NDA 216774 received Tentative Approval under 21 CFR 314.105 with final approval subject to expiration of a period of patent protection and/or exclusivity.

On September 29, 2023, the Applicant submitted a request for final approval of Alvaiz tablets.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

[a] Mehta, H. Label and Labeling for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. OSE RCM No.: 2021-2343.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the proposed Alvaiz (eltrombopag) tablet product has the same active ingredient, dosage form, frequency, and route of administration as the listed drug, Promacta. We note the proposed product differs in strength due to the salt of the proposed product (9 mg, 18 mg, 36 mg, and 54 mg vs. 12.5 mg, 25 mg, 50 mg, and 75 mg) and therefore differs in dose. Alvaiz is being proposed for the same indications as the listed drug Promacta except for the indication 'in combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia' due to exclusivity. In addition, the pediatric age range differs between the two products for the treatment of thrombocytopenia (Alvaiz is indicated for 6 years and older and Promacta is indicated for 1 year and older). In addition, listed drug Promacta is available as a for oral suspension dosage form in 12.5 mg per packet and 25 mg per packet strengths.

Alvaiz is being proposed in different strengths from the listed drug and we note a not substitutable statement in the PI and container labels.

(b) (4)

We note that the currently proposed indication has been revised to be limited to "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". We defer to the Division on the acceptability of the proposed product in pediatric patients.

We performed a risk assessment of the proposed PI, MG, and container labels for Alvaiz tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors.

We note that the proposed MG was updated (since our last review[b]) to add "Dispense with Medication Guide available at: www.tevausa.com/medguides", to update the indication to "…children 6 years of age and older" and to add "Tell your healthcare provider if your or your

[b] Mehta, H. Label and Labeling for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. OSE RCM No.: 2021-2343.

child are not able to swallow ALVAIZ tablets whole. You will need to take a different medicine." In addition, we note that the MG states "Keep ALVAIZ in the bottle given to you." We reached out to Office of Pharmaceutical Quality (OPQ) to clarify if the product requires to be stored and dispensed in the original container. OPQ confirmed the product is stable (i.e., not moisture or light sensitive) and does not object to the statement "Keep ALVAIZ in the bottle given to you." without further rationale. We find the proposed MG acceptable from a medication error perspective.

We note that the proposed PI was updated (since our last review[c]) to:

- Add not substitutable statement in HPI and Section 2
- Revise dosing information (i.e., removed (b) (4) and updated do not exceed (b) (4) mg per day to 108 mg per day for aplastic anemia indication)
- Add new Section 2.1 for Important Dosage Information
- Remove statement (b) (4)
- Remove equivalency statements in Section 3
- Remove statement (b) (4) " in Section 16.
- Add "Dispense with Medication Guide available at: www.tevausa.com/medguides" in Section 16

We note that the container labels were updated (from our last review[d]) to:

- Relocate the equivalency and MG statement from PDP to side panel
- Relocate Rx Only to top right of the PDP
- Remove the (b) (4) on side panel
- Add "Swallow tablet whole…" and not substitutable statements on the PDP
- Add product identifier including placeholder for lot number and expiration date (MM/YYYY)

In addition, we note the containers labels contain an asterisk next to the strength statement and the dosage form is included inside the parenthesis with the established name. We reached out to OPQ and confirmed these are acceptable. In addition, OPQ plans to provide a comment to the Applicant indicating that if they intend to seek marketing approval for a different dosage form in the future, the dosage form should not be part of the established name.

[c] Mehta, H. Label and Labeling for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. OSE RCM No.: 2021-2343

[d] Mehta, H. Label and Labeling for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. OSE RCM No.: 2021-2343

Our evaluation of the proposed PI and container labels found they are unacceptable from a medication error perspective. For the Division, we note the route of administration is not included in the dosing information and the administration information lacks clarity. For the Applicant, we note the MG statement on the side panel, the dosage statement can be revised and expiration date includes a 2-letter abbreviation. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

The proposed MG is acceptable from a medication error perspective. However, we identified areas in the proposed container labels and PI that can be improved to promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Teva to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlight of Prescribing Information (HPI)
    1. As currently presented the route of administration is not presented in the dosing information. We recommend including the route of administration in the dosing information to minimize administration errors. For example, revise to:
        a. Persistent or Chronic ITP: Initiate ALVAIZ at 36 mg orally once daily for most adult and pediatric patients 6 years and older.
        b. Chronic Hepatitis C-associated Thrombocytopenia: Initiate ALVAIZ at 18 mg orally once daily for all patients.
        c. Refractory Severe Aplastic Anemia: Initiate ALVAIZ at 36 mg orally once daily.

B. Prescribing Information
    1. Dosage and Administration Section
        a. As currently presented, Section 2.1 *Important Information* states "Eltrombopag is available (b)(4) different indications, dosage forms, and tablet strengths." For clarity, we recommend revising to "Eltrombopag is available for different indications and in different dosage forms and tablet strengths."
        b. As currently presented, Section 2.1 *Important Information* states "ALVAIZ is not substitutable with other eltrombopag products on a milligram per milligram basis."; however it does not indicate the reason the product is not substitutable with other eltrombopag products. This information may be helpful for prescribers. For added clarity, we recommend revising the statement to "ALVAIZ is not substitutable with other eltrombopag products on a milligram per milligram basis due to [reason]."
        c. As currently presented the route of administration is not presented in the dosing information. We recommend including the route of administration

in the dosing information to minimize administration errors. For example, revise to:

i. Section 2.2 *Recommended Dosage for Persistent or Chronic Immune Thrombocytopenia*: "Initial Dose Regimen: Adult and Pediatric Patients 6 Years and Older with ITP: Initiate ALVAIZ at a dose of 36 mg orally once daily…"
ii. Section 2.3 *Recommended Dosage for Chronic Hepatitis C-associated Thrombocytopenia*: "Initial Dose Regimen: Initiate ALVAIZ at a dose of 18 mg orally once daily…"
iii. Section 2.4 *Recommended Dosage for Refractory Severe Aplastic Anemia*: "Initial Dose Regimen: Initiate ALVAIZ at a dose of 36 mg orally once daily…"

d. As currently presented, Section 2.1 *Important Information* states "Patients must be able to swallow ALVAIZ tablets whole." However, Section 2.5 *Administration* states, "Do not split, chew, or crush tablets and mix with food or liquids." and the container labels state, "Swallow tablets whole. Do not split, chew, or crush tablets." For consistency throughout the PI and with the container labels, we recommend revising the statement in Section 2.5 *Administration* to, "Swallow tablets whole. Do not split, chew, or crush tablets and mix with food or liquids.

4.2 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The Medication Guide (MG) statement is located on a side panel. Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d). To ensure its prominence, we recommend relocating the MG statement to the principal display panel (PDP) where the "Swallow tablets whole…" statement is currently. In addition, consider relocating the "Swallow tablets whole. Do not split, chew, or crush tablets." statement to the where the MG statement is on the side panel.
2. As currently presented, the statement of dosage reads "(b) (4) " For consistency, we recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information."

3. As currently presented, the expiration date includes a 2-letter abbreviation (e.g., MM/YYYY). Clarify whether MM is intended to indicate a 2-letter abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). 2-letter abbreviations have led to confusion for the months of March vs May and June vs July. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alvaiz received on September 29, 2023 from Teva Pharmaceuticals Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
Initial Approval Date	N/A	11/20/2008 (Tablet) 08/24/2015 (Oral Suspension)
Active Ingredient	eltrombopag	

[e] Promacta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. March 2023. [cited 2023 OCT 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022291s037,207027s017lbl.pdf.

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
Indication	ALVAIZ is a thrombopoietin receptor agonist indicated: • 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	PROMACTA is a thrombopoietin receptor agonist indicated: • 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. • 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. • in combination with standard immunosuppressive therapy for the first-line

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
	immunosuppressive therapy. Limitations of Use: • ALVAIZ is 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.	treatment of adult and pediatric patients 2 years and older with severe aplastic anemia. • for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Limitations of Use: • PROMACTA is 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.
Route of Administration	oral	
Dosage Form	tablets	Tablets; For oral suspension
Strength	9 mg, 18 mg, 36 mg, and 54 mg	• Tablets: 12.5 mg, 25 mg, 50 mg, and 75 mg • For oral suspension: 12.5 mg and 25 mg

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
Dose and Frequency	• ALVAIZ is not substitutable with other eltrombopag products on a milligram per milligram basis. • Take ALVAIZ without a meal or with a meal low in calcium (≤ 50 mg). Take ALVAIZ at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements. • Persistent or Chronic ITP: Initiate ALVAIZ at 36 mg once daily for most adult and pediatric patients 6 years and older. Dose reductions are needed for patients with hepatic impairment and some patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 109/L. Do not exceed 54 mg per day. • Chronic Hepatitis C-associated Thrombocytopenia: Initiate ALVAIZ at 18 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 72 mg. • Refractory Severe Aplastic Anemia: Initiate ALVAIZ at 36 mg once daily. Reduce	• Take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg). Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements. • Persistent or Chronic ITP: Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 109/L. Do not exceed 75 mg per day. • Chronic Hepatitis C-associated Thrombocytopenia: Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. • First-line Severe Aplastic Anemia: Initiate PROMACTA once daily at 2.5 mg/kg (in pediatric

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
	initial dose in patients with hepatic impairment or patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than 50 x 109/L. Do not exceed 108 mg per day.	patients aged 2 to 5 years old), 75 mg (pediatric patients aged 6 to 11 years old), or 150 mg for patients aged 12 years and older concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of East-/Southeast-Asian ancestry. Modify dosage for toxicity or elevated platelet counts. • Refractory Severe Aplastic Anemia: Initiate PROMACTA at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of East-/Southeast-Asian ancestry. Adjust to maintain platelet count greater than 50 x 109/L. Do not exceed 150 mg per day.

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
How Supplied	ALVAIZ (eltrombopag tablets) is for oral administration and are available as follows. 9 mg - Blue, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z9” on the other side. The tablets are available in bottles of 14 (NDC 0480-3273-41) and 180 (NDC 0480-3273-86). 18 mg - Off-white, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z18” on the other side. The tablets are available in bottles of 14 (NDC 0480-3274-41) and 180 (NDC 0480-3274-86). 36 mg - Red, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z36” on the other side. The tablets are available in bottles of 14 (NDC 0480-3275-41) and 180 (NDC 0480-3275-86). 54 mg - Orange, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z54” on the other side. The tablets are available in bottles of 14 (NDC 0480-3276-41) and 180 (NDC 0480-3276-86).	16.1 Tablets • The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with “GS MZ1” and 12.5 on one side and are available in bottles of 30: NDC 0078-0684-15 • The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with “GS NX3” and 25 on one side and are available in bottles of 30: NDC 0078-0685-15 • The 50-mg tablets are round, biconvex, blue, film-coated tablets debossed with “GS UFU” and 50 on one side and are available: o Bottles of 14 NDC 0078-0686-55 o Bottles of 30 NDC 0078-0686-15 • The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with “GS FFS” and 75 on one side and are available in bottles of 30: NDC 0078-0687-15 16.2 For Oral Suspension • The 12.5-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, copackaged in a kit with a 40-cc reconstitution vessel, a threaded closure with

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
		syringe-port capability, and 30 single-use oral dosing syringes. Each kit (NDC 0078-0972-61) contains 30 packets: NDC 0078-0972-19 • The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, copackaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes. Each kit (NDC 0078-0697-61) contains 30 packets: NDC 0078-0697-19

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta [e]
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Tablets: Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Dispense in original bottle. For Oral Suspension: Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Throw away (discard) the mixture if not used within 30 minutes.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 06, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, eltrombopag. Our search identified 2 previous reviews (see Table 3 below), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. Comparison of eltrombopag products

Application	Applicant	Strength	Status	OSE Review
NDA 022291 NDA 207027 Promacta (eltrombopag)	Novartis	Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg Oral suspension: 12.5 mg and 25 mg packets	Approved 11/20/2008 (tablets) Approved 08/24/2015 (packets for oral suspension)	2023-4857[f]
NDA 216774 Alvaiz (eltrombopag)	Teva	Tablets: 9 mg, 18 mg, 36 mg, and 54 mg	Subject of this review	2021-2343[g]

[f] Black, S. Label and Labeling Review for Promacta (NDA 022291/S-038). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 31. OSE RCM No.: 2023-4857

[g] Mehta, H. Label and Labeling for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. OSE RCM No.: 2021-2343

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Alvaiz labels and labeling submitted by Teva Pharmaceuticals Inc.

- Container label received on September 29, 2023
- Prescribing Information (Image not shown) received on September 29, 2023, available from \\CDSESUB1\EVSPROD\nda216774\0020\m1\us\draft-pi-clean-alvaiz.pdf
- Medication Guide (Image not shown) received on September 29, 2023, available from \\CDSESUB1\EVSPROD\nda216774\0020\m1\us\draft-mg-clean-alvaiz.pdf

F.2 Label and Labeling Images

Container labels

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 13, 2023

To: Carleveva Thompson, MS, Regulatory Project Manager,
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALVAIZ™ (eltrombopag tablets), for oral use

NDA: 216774

Background:
In response to DNH's consult request dated October 31, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for ALVAIZ™ (eltrombopag tablets), for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 3, 2023, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on November 8, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 29, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 8, 2023
To:	Carleveva Thompson, MS Senior Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ALVAIZ (eltrombopag tablets)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216774
Applicant:	Teva Pharmaceuticals, Inc.

1 INTRODUCTION

On September 29, 2023, Teva Pharmaceuticals, Inc. resubmitted for the Agency's review a proposed New Drug Application (NDA) 216774 for ALVAIZ (eltrombopag tablets) in response to the Agency's tentative approval letter dated October 3, 2022. With this resubmission, the Applicant requests final approval of this 505(b)(2) application, which references the listed drug PROMACTA (eltrombopag) tablets (NDA 022291). The proposed indications for ALVAIZ (eltromopag tablets) are:

- 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on October 31, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ALVAIZ (eltrombopag tablets).

2 MATERIAL REVIEWED

- Draft ALVAIZ (eltrombopag tablets) MG received on September 29, 2023, and received by DMPP and OPDP on November 3, 2023.
- Draft ALVAIZ (eltrombopag tablets) Prescribing Information (PI) received on September 29, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 3, 2023.
- Approved PROMACTA (eltrombopag) tablets comparator labeling dated March 9, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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11/08/2023 02:40:42 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 29, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216774
Product Name and Strength:	Alvaiz (eltrombopag) Tablets, 9 mg, 18 mg, 36 mg, and 54 mg
Applicant/Sponsor Name:	Teva Pharmaceuticals, Inc.
OSE RCM #:	2021-2343-1
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on September 27, 2022 for Alvaiz. We reviewed the revised container labels for Alvaiz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Mehta, H. Label and Labeling Review for Alvaiz (NDA 216774). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 14. RCM No.: 2021-2343.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 9, 2022
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Nonmalignant Hematology**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Alvaiz (eltrombopag tablets)
Route:	for oral use
Application Type/Number:	NDA 216774
Applicant:	Teva Pharmaceuticals, Inc.

1 INTRODUCTION

On December 3, 2021, Teva Pharmaceuticals, Inc. submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 216774 for ALVAIZ (eltrombopag tablets). The Reference Listed Product is PROMAXTA (eltrombopag tablets) [NDA 022291]. The Applicant is seeking approval for a drug product that contains a different salt of the active ingredient as well as different strengths.

The proposed indications for ALVAIZ (eltrombopag tablets) are as follows:

- 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on February 3, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) ALVAIZ (eltrombopag tablets).

2 MATERIAL REVIEWED

- Draft ALVAIZ (eltrombopag tablets) MG received on December 3, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on August 30, 2022.
- Draft ALVAIZ (eltrombopag tablets) Prescribing Information (PI) received on December 3, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on August 30, 2022.
- Approved PROMACTA (eltrombopag) tablets Reference Listed Product [NDA 022291] labeling dated March 31, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 8, 2022

To: Carleveva Thompson, MS, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALVAIZ™ (eltrombopag tablets), for oral use

NDA: 216774

In response to DNH's consult request dated February 3, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG) and carton and container labeling for the original NDA submission for ALVAIZ™ (eltrombopag tablets), for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Carleveva Thompson) on August 30, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed MG will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 13, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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MELISSA KHASHEI
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 14, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216774
Product Name, Dosage Form, and Strength:	Alvaiz (eltrombopag) tablets, 9 mg, 18 mg, 36 mg, and 54 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Teva
FDA Received Date:	December 3, 2021 and July 13, 2022
OSE RCM #:	2021-2343
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Alvaiz (eltrombopag) tablets, we reviewed the proposed Alvaiz prescribing information (PI), medication guide (MG), and container labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Teva Pharmaceuticals Inc. (Teva) submitted Alvaiz (eltrombopag) NDA 216774 on December 3, 2021, as a 505(b)(2) application which relies upon the listed drug, Promacta (eltrombopag) tablets under NDA 022291. Promacta (eltrombopag) is currently marketed as 12.5 mg, 25 mg, 50 mg, and 75 mg tablets under NDA 022291 and as 12.5 mg and 25 mg for oral suspension packets under NDA 207027.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the proposed Alvaiz (eltrombopag) tablet product has the same active ingredient, dosage form, frequency, and route of administration as the listed drug, Promacta. We note the proposed product differs in strength due to the salt of the proposed product (9 mg, 18 mg, 36 mg, and 54 mg vs. 12.5 mg, 25 mg, 50 mg, and 75 mg) and therefore differs in dose. Alvaiz is being proposed for the same indications as the listed drug Promacta except for the indication 'in combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia' due to exclusivity. In addition, the listed drug Promacta is available as a for oral suspension dosage form in 12.5 mg per packet and 25 mg per packet strengths.

As Alvaiz is being proposed in different strengths from the listed drug, we recommend including a not substitutable statement in the PI and container labels.

(b) (4)

We performed a risk assessment of the proposed PI, MG, and container labels for Alvaiz tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. We find the proposed MG acceptable from a medication error perspective. We note the container label states (b) (4) along with the standard medication guide statement. (b) (4)

For the Division, we note Section 2.1 mentions (b) (4) which may cause confusion (b) (4) For the Applicant, the format of expiration date is not defined, and the product identifier information is missing. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Teva to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlights of Prescribing Information

    1. To avoid substitution errors and overdosage, we recommend including the statement "Alvaiz is not substitutable with other eltrombopag products on a milligram-per-milligram basis.".

B. Prescribing Information

    1. Dosage and Administration Section

a. To avoid substitution errors and overdosage, we recommend including the statement “Alvaiz is not substitutable with other eltrombopag products on a milligram-per-milligram basis.”.

b. Section 2.1 contains a statement regarding (b) (4) (b) (4) We note this product is only being proposed in the tablet formulation. As such, we recommend this statement be removed as it may cause confusion.

4.2 RECOMMENDATIONS FOR TEVA

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As the proposed product differs in strength from the listed drug, we recommend including a statement on the principal display panel stating it is not substitutable with other eltrombopag products. We recommend adding “Alvaiz is NOT substitutable with other eltrombopag products on a milligram-per-milligram basis.”.

2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

3. We note the equivalency statement on the principal display panel contains a trailing zero. We recommend removing the trailing zero (e.g. 11.10 mg) to avoid a ten-fold misinterpretation.

4. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product

identifier requirements apply to your product's labeling. The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alvaiz received on December 3, 2021 from Teva, and the listed drug (LD).

Table 2. Relevant Product Information for Alvaiz and the Listed Drug		
Product Name	Alvaiz	Promacta[a]
Initial Approval Date	N/A	November 20, 2008
Active Ingredient	eltrombopag	
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. 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	• 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. 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

[a] Promacta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 JUN 28. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022291

	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	prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy • in combination with standard immunosuppressive therapy for the first line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia • for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy
Route of Administration	oral	
Dosage Form	tablets	Tablets and for oral suspension
Strength	9 mg, 18 mg, 36 mg, and 54 mg	Tablets: 12.5 mg, 25 mg, 50 mg, and 75 mg For Oral Suspension: 12.5 mg and 25 mg
Dose and Frequency	• <u>Persistent or chronic ITP:</u> Initiate ALVAIZ at 36 mg once daily for most adult and pediatric patients 6 years and older, (b) (4) (b) (4) (b) (4) Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 54 mg per day. • <u>Chronic Hepatitis C-associated Thrombocytopenia:</u> Initiate ALVAIZ at 18 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do	•Take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg). Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements. •Persistent or chronic ITP: Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 109/L. Do not exceed 75 mg per day.

	not exceed a daily dose of 72 mg. • Refractory Severe Aplastic Anemia: Initiate ALVAIZ at 36 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed (b) (4) mg per day.	•Chronic Hepatitis C-associated Thrombocytopenia: Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. •First-line Severe Aplastic Anemia: Initiate PROMACTA once daily at 2.5 mg/kg (in pediatric patients aged 2 to 5 years old), 75 mg (pediatric patients aged 6 to 11 years old), or 150 mg for patients aged 12 years and older concurrently with standard immunosuppressive therapy. Reduce initial dose in patients of Asian ancestry. Modify dosage for toxicity or elevated platelet counts. •Refractory Severe Aplastic Anemia: Initiate PROMACTA at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50 x 109/L. Do not exceed 150 mg per day.
How Supplied	9 mg - Blue, round, biconvex, film-coated tablets debossed with "TV" on one side and "Z9" on the other side. The tablets are available in bottles of 14 (NDC 0480-3273-41) and 180 (NDC 0480-3273-86). 18 mg - Off-white, round, biconvex, film-coated tablets debossed with "TV" on one side and "Z18" on the other side.	The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side and are available in bottles of 30: NDC 0078-0684-15 The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side and are available in bottles of 30: NDC 0078-0685-15 The 50-mg tablets are round, biconvex, blue, film-coated tablets

	The tablets are available in bottles of 14 (NDC 0480-3274-41) and 180 (NDC 0480-3274-86). 36 mg - Red, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z36” on the other side. The tablets are available in bottles of 14 (NDC 0480-3275-41) and 180 (NDC 0480-3275-86). 54 mg - Orange, round, biconvex, film-coated tablets debossed with “TV” on one side and “Z54” on the other side. The tablets are available in bottles of 14 (NDC 0480-3276-41) and 180 (NDC 0480-3276-86).	debossed with GS UFU and 50 on one side and are available: Bottles of 14: NDC 0078-0686-55 Bottles of 30: NDC 0078-0686-15 The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side and are available in bottles of 30: NDC 0078-0687-15 The 12.5-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes. Each kit (NDC 0078-0972-61) contains 30 packets: NDC 0078-0972-19 The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, a threaded closure with syringe-port capability, and 30 single-use oral dosing syringes. Each kit (NDC 0078-0697-61) contains 30 packets: NDC 0078-0697-19
Storage	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].	Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Dispense in original bottle.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 28, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Alvaiz' and 'NDA 216774'. Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Alvaiz labels and labeling submitted by Teva.

- Container labels received on July 13, 2022
- Prescribing Information (Image not shown) received on December 3, 2021, available from \\CDSESUB1\evsprod\nda216774\0001\m1\us\draft-pi-alvaiz.pdf
- Medication Guide received on December 3, 2021, available from \\CDSESUB1\evsprod\nda216774\0001\m1\us\draft-mg-alvaiz.pdf

G.2 Label and Labeling Images

Container Labels

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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