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Subject: Eltrombopag (Promacta®, Alvaiz™)

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DESCRIPTION:

Eltrombopag (Promacta®, Alvaiz™) is an oral small molecule thrombopoietin (TPO) mimetic that increases platelet production by binding and activating the TPO receptor, similar to endogenous TPO. The US Food and Drug Administration (FDA) granted the accelerated approval for eltrombopag (Promacta) for treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia purpura (ITP) whose disease was refractory to corticosteroids, immunoglobulins, or splenectomy. Alvaiz is also FDA approved for persistent or chronic immune thrombocytopenia purpura (ITP) in pediatric patients 6 years and older whose disease was refractory to corticosteroids, immunoglobulins, or splenectomy. The FDA also approved eltrombopag (Promacta, Alvaiz) for the treatment of thrombocytopenia in persons with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. The FDA later approved the use of eltrombopag (Promacta, Alvaiz) for patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Eltrombopag (Promacta) is also FDA approved for the initial treatment of severe aplastic anemia in combination with standard immunosuppressive therapy (antithymocyte globulin and cyclosporine).

ITP is an autoimmune disorder characterized by a destruction of otherwise normal platelets and frequently occurs without a known or identifiable cause; it is considered a diagnosis of exclusion as there are no diagnostic tests to confirm ITP. The American Society of Hematology (ASH) published a guideline outlining the diagnosis and management of ITP. Treatment of newly diagnosed ITP is recommended when the platelet count is less than 30,000. Initial treatment options for ITP include corticosteroids, IVIG, or anti-D.

Persons who are unresponsive to or relapse after initial corticosteroid therapy are considered to have chronic ITP. In this setting, the following treatment options are recommended:

- Splenectomy
- Thrombopoietin receptor agonists (e.g., eltrombopag [Promacta] or romiplostim [Nplate])
- Rituximab (Rituxan)

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for myelodysplastic syndrome (MDS) support use of eltrombopag (Promacta) in patients with lower risk disease (low or intermediate-1 category International Prognostic Scoring System (IPSS), Revised International Prognostic Scoring System (IPSS-R) very low, low, or intermediate category, or WHO-classification based prognostic scoring system (WPSS) very low, low, or intermediate category). Eltrombopag (Promacta, Alvaiz) is also supported by NCCN for the treatment of prolonged thrombocytopenia in patients with post-allogeneic transplant and poor graft function.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

I. Initiation of eltrombopag (Promacta®) **meets the definition of medical necessity** when used to treat thrombocytopenia associated with **ONE** of the following conditions:
   A. Persistent or Chronic immune (idiopathic) thrombocytopenic purpura (ITP) and **ALL** of the following are met:
      1. The member has demonstrated an insufficient response to **EITHER** of the following:
         a. Adequate trial of corticosteroids (e.g., prednisone 1-2 mg/kg for 2-4 weeks)
         b. Immunoglobulins therapy (e.g., intravenous immune globulin [IVIG])
      2. The member does not have chronic liver disease
      3. **ONE** of the following:
         a. The member's platelet count is less than 30,000
         b. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
      4. Eltrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
      5. The dosage does not exceed 75 mg daily and will be achieved using the fewest number of tablets or packets per day.
   B. Chronic hepatitis C virus (HCV) infection and **ALL** of the following are met:
      1. The member's platelet count is less than 75,000
      2. The intent of eltrombopag therapy is one of the following:
         a. To allow the member to initiate interferon-based therapy

b. To allow the member to maintain interferon based therapy

3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dosage does not exceed 100 mg daily and will be achieved using the fewest number of tablets or packets per day.

C. Severe aplastic anemia (SAA) and ALL of the following are met:

1. **ONE** of the following:
    a. The member's platelet count is less than 30,000
    b. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
2. **ONE** of the following:
    a. The member has demonstrated an insufficient response to immunosuppressive therapy (e.g.,anti-thymocyte globulin, cyclosporine)
    b. The member will receive treatment in combination with immunosuppressive therapy (i.e.,antithymocyte globulin, cyclosporine)
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dosage does not exceed 150 mg daily and will be achieved using the fewest number of tablets or packets per day.

D. Low Risk Myelodysplastic Syndrome (MDS) (i.e., IPSS low and intermediate-1 categories; IPSS-R: Very low, low, intermediate categories; WPSS Very low, low, and intermediate categories) and **ALL** of the following:

1. **ONE** of the following:
    i. The member's platelet count is less than 30,000
    ii. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
2. Eltrombopag is used as a single agent or in combination with one of the following:
    i. Anti-thymocyte globulin
    ii. Cyclosporine
    iii. Anti-thymocyte globulin and cyclosporine
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim, avatrombopag, lusutrombopag)
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets or packets per day.

E. Thrombocytopenia post-hematopoietic cell transplant

1. The member's platelet count is less than 100,000 for 3 or more weeks following hematopoietic cell transplant
2. Other potential causes of thrombocytopenia have been ruled out
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim, avatrombopag, lusutrombopag)

4.The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets or packets per day

Approval duration: 6 months

II. Continuation of therapy eltrombopag (Promacta®) **meets the definition of medical necessity** when used for treatment of thrombocytopenia associated with one of the following conditions and **ALL** of the condition-specific criteria are met:

A. Persistent or Chronic ITP

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of persistent or chronic ITP, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed 75 mg daily and will be achieved using the fewest number of tablets or packets per day.

B. Chronic HCV infection

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of chronic HCV infection, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. The member is receiving concomitant interferon-based therapy
4. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
5. The dose does not exceed 100 mg daily and will be achieved using the fewest number of tablets or packets per day.

C. Severe aplastic anemia

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of severe aplastic anemia, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed 150 mg daily and will be achieved using the fewest number of tablets or packets per day.

D. Low Risk Myelodysplastic Syndrome (MDS) and **ALL** of the following:

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of MDS, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets or packets per day.

E. Thrombocytopenia post-hematopoietic cell transplant and **ALL** of the following:

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of thrombocytopenia post-hematopoietic cell transplant, OR the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets or packets per day.

Approval duration: 1 year

III. Initiation of eltrombopag (Alvaiz™) **meets the definition of medical necessity** when used to treat thrombocytopenia associated with **ONE** of the following conditions and the member had an inadequate response to Promacta – documentation must be submitted:

A. Persistent or Chronic immune (idiopathic) thrombocytopenic purpura (ITP) and **ALL** of the following are met:

1. The member has demonstrated an insufficient response to **EITHER** of the following:
   a. Adequate trial of corticosteroids (e.g., prednisone 1-2 mg/kg for 2-4 weeks)
   b. Immunoglobulins therapy (e.g., intravenous immune globulin [IVIG])
2. The member does not have chronic liver disease
3. **ONE** of the following:
   a. The member's platelet count is less than 30,000
   b. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
4. Eltrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
5. The dosage does not exceed 54 mg daily and will be achieved using the fewest number of tablets per day.

B. Chronic hepatitis C virus (HCV) infection and **ALL** of the following are met:

1. The member's platelet count is less than 75,000
2. The intent of eltrombopag therapy is one of the following:

a. To allow the member to initiate interferon-based therapy
b. To allow the member to maintain interferon based therapy

3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dosage does not exceed 72 mg daily and will be achieved using the fewest number of tablets per day.

C. Severe aplastic anemia (SAA) and **ALL** of the following are met:
1. **ONE** of the following:
a. The member's platelet count is less than 30,000
b. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
2. The member has demonstrated an insufficient response to immunosuppressive therapy (e.g.,anti-thymocyte globulin, cyclosporine)
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dosage does not exceed 108 mg daily and will be achieved using the fewest number of tablets per day.

D. Low Risk Myelodysplastic Syndrome (MDS) (i.e., IPSS low and intermediate-1 categories; IPSS-R: Very low, low, intermediate categories; WPSS Very low, low, and intermediate categories) and ALL of the following:
1. **ONE** of the following:
i. The member's platelet count is less than 30,000
ii. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
2. Eltrombopag is used as a single agent or in combination with one of the following:
i. Anti-thymocyte globulin
ii. Cyclosporine
iii. Anti-thymocyte globulin and cyclosporine
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim, avatrombopag, lusutrombopag)
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets or packets per day

E. Thrombocytopenia post-hematopoietic cell transplant
1. The member's platelet count is less than 100,000 for 3 or more weeks following hematopoietic cell transplant
2. Other potential causes of thrombocytopenia have been ruled out
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim, avatrombopag, lusutrombopag)
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets per day

Approval duration: 6 months

IV. Continuation of therapy eltrombopag (Alvaiz™) **meets the definition of medical necessity** when used for treatment of thrombocytopenia associated with one of the following conditions and **ALL** of the condition-specific criteria are met:

A. Persistent or Chronic ITP

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of persistent or chronic ITP, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed 54 mg daily and will be achieved using the fewest number of tablets per day.

B. Chronic HCV infection

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of chronic HCV infection, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. The member is receiving concomitant interferon-based therapy
4. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
5. The dose does not exceed 72 mg daily and will be achieved using the fewest number of tablets per day.

C. Severe aplastic anemia

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of severe aplastic anemia, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed 108 mg daily and will be achieved using the fewest number of tablets per day.

D. Low Risk Myelodysplastic Syndrome (MDS) and **ALL** of the following:

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of MDS, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets per day.

E. Thrombocytopenia post-hematopoietic cell transplant and **ALL** of the following:

1. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for eltrombopag for the treatment of thrombocytopenia post-hematopoietic cell transplant, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline – documentation must be submitted
3. Eltrombopag is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], avatrombopag [Doptelet], lusutrombopag [Mulpleta])
4. The dose does not exceed the maximum FDA-approved dose and will be achieved using the fewest number of tablets per day.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: eltrombopag is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) with an insufficient response to corticosteroids, immunoglobulins, or splenectomy. It is also indicated for thrombocytopenia in patients with chronic hepatitis C virus (HCV) to allow the initiation and maintenance of interferon-based therapy. Eltrombopag is indicated for patients with severe aplastic anemia in adult and pediatric patients 2 years and older as first line therapy (Promacta only) in combination with immunosuppressants (antithymocyte globulin and cyclosporine) and as subsequent therapy (Promacta and Alvaiz) in those who have had an insufficient response to immunosuppressive therapy.

Dose adjustments are based upon the platelet count response. Do not use eltrombopag in an attempt to normalize platelet counts.

Eltrombopag should be administered without a meal or with a meal low in calcium (≤50 mg). Take at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc. Do not split, chew or crush tablets. See prescribing information for preparation of the oral suspension.

ITP

Promacta

- Initial dose: 50 mg once daily for most adult patients and pediatric patents 6 years of age and older and 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed in persons of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

  - East Asian ancestry, initiate eltrombopag at a reduced dose of 25 mg once daily.

  - Mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 25 mg once daily.

- East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 12.5 mg once daily.

- Use the lowest dose of eltrombopag to achieve and maintain a platelet count ≥50,000 as necessary to reduce the risk for bleeding.
- Do not exceed a dose of 75 mg daily.
- Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 1. During therapy with eltrombopag, assess CBCs with differentials, including platelet count, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

Table 1

Dose Adjustments of Eltrombopag in Adults with ITP (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**
<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg to a maximum of 75 mg/day For persons taking 12.5 mg once daily; increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥200,000 to ≤400,000 at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For persons taking 25 mg once daily, decrease the dose to 12.5 mg daily.
>400,000	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For persons taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- In ITP patients with hepatic impairment, after initiating eltrombopag or after any subsequent dosing increase, wait 3 weeks before increasing the dose.
- Discontinue eltrombopag if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with eltrombopag at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of eltrombopag.

HCV

Promacta

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use eltrombopag to normalize platelet counts.

- Initial Dose: Initiate eltrombopag at a dose of 25 mg once daily.
- Monitoring and Dose Adjustment: Adjust the dose of eltrombopag in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.
- During antiviral therapy, adjust the dose of eltrombopag to avoid dose reductions of peginterferon. Monitor CBCs with differentials (including platelet counts) weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2

Dose Adjustments of Eltrombopag in Adults with Chronic HCV (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**
<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg to a maximum of 100 mg/day
≥200,000 to ≤400,000 at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg. For persons taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.
- Eltrombopag should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation of eltrombopag.

SAA

Promacta

First line therapy:

Initiate concurrently with standard immunosuppressive therapy (antithymocyte globulin and cyclosporine). For patients 12 years and older initiate at 150 mg once daily for 6 months. For pediatric patients 6 to 11 years initiate at 75 mg once daily for 6 months. For pediatric patients aged 2 to 5 years 2.5 mg/kg once daily for 6 months.

See prescribing information for initial dose adjustment for patients of Asian ancestry, or those with mild moderate, or severe hepatic impairment. Adjust initial dose if baseline ALT or AST levels are abnormal.

The dose should be modified based on platelet counts, ALT, or AST elevations. The duration of treatment is 6 months.

Refractory SAA:

Promacta

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to maintain a hematologic response. Dose adjustments are based upon the platelet count response. Hematologic response requires dose titration.

- Initial dose: 50 mg once daily, except in persons of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

    - East Asian ancestry, initiate eltrombopag at a reduced dose of 25 mg once daily.

    - Mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 25 mg once daily.

- After initiating eltrombopag,adjust the dose every 2 weeks as necessary to achieve and maintain a platelet count ≥50,000.
- Do not exceed a dose of 150 mg daily.
- Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 3. During therapy with eltrombopag, assess CBCs with differential, including platelet count, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

Table 3

Dose Adjustments of Eltrombopag in Adults with Refractory SAA (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**
<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 50 mg to a maximum of 150 mg/day For persons taking 25 mg once daily; increase the dose to 50 mg daily before increasing the dose amount by 50 mg.

≥200,000 to ≤400,000 at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000	Stop eltrombopag for 1 week. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 50 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%. If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to less than 30,000, hemoglobin to less than 9 g/dL, or ANC to less than 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.
- Discontinue eltrombopag if no hematologic response has occurred after 16 weeks of therapy. If new cytogenetic abnormalities are observed, consider discontinuation of eltrombopag. Excessive platelet count responses, as outlined in Table 3, or important liver test abnormalities also necessitate discontinuation of eltrombopag.

ITP

Alvaiz

- Initial dose: 36 mg once daily for most adult patients and pediatric patents 6 years of age and older. Dose reductions are needed in persons of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

  - East Asian ancestry, initiate eltrombopag at a reduced dose of 18 mg once daily.

  - Mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 18 mg once daily.

  - East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 9 mg once daily.

- Use the lowest dose of eltrombopag to achieve and maintain a platelet count ≥50,000 as necessary to reduce the risk for bleeding.
- Do not exceed a dose of 54 mg daily.
- Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 1. During therapy with eltrombopag, assess CBCs with differentials, including platelet count, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

Table 1

Dose Adjustments of Eltrombopag in Adults with ITP (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**
<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 18 mg to a maximum of 54 mg/day

	For persons taking 9 mg once daily; increase the dose to 18 mg daily before increasing the dose amount by 18 mg.
≥200,000 to ≤400,000 at any time	Decrease the daily dose by 18 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For persons taking 18 mg once daily, decrease the dose to 9 mg daily.
>400,000	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 18 mg. For persons taking 18 mg once daily, reinitiate therapy at a daily dose of 9 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- In ITP patients with hepatic impairment, after initiating eltrombopag or after any subsequent dosing increase, wait 3 weeks before increasing the dose.
- Discontinue eltrombopag if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with eltrombopag at the maximum daily dose of 54 mg. Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of eltrombopag.

HCV

Promacta

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use eltrombopag to normalize platelet counts.

- Initial Dose: Initiate eltrombopag at a dose of 18 mg once daily.
- Monitoring and Dose Adjustment: Adjust the dose of eltrombopag in 18 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.
- During antiviral therapy, adjust the dose of eltrombopag to avoid dose reductions of peginterferon. Monitor CBCs with differentials (including platelet counts) weekly during antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 72 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2

Dose Adjustments of Eltrombopag in Adults with Chronic HCV (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**
<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 18 mg to a maximum of 72 mg/day
≥200,000 to ≤400,000 at any time	Decrease the daily dose by 18 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.

>400,000	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 18 mg. For persons taking 18 mg once daily, reinitiate therapy at a daily dose of 9 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- Discontinuation: The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.
- Eltrombopag should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation of eltrombopag.

SAA

Promacta

Refractory SAA:

Promacta

Use the lowest dose of eltrombopag to achieve and maintain a platelet count necessary to maintain a hematologic response. Dose adjustments are based upon the platelet count response. Hematologic response requires dose titration.

- Initial dose: 36 mg once daily, except in persons of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

  - East Asian ancestry, initiate eltrombopag at a reduced dose of 18 mg once daily.

  - Mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate eltrombopag at a reduced dose of 18 mg once daily.

- After initiating eltrombopag,adjust the dose every 2 weeks as necessary to achieve and maintain a platelet count ≥50,000.
- Do not exceed a dose of 108 mg daily.
- Monitor clinical hematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 3. During therapy with eltrombopag, assess CBCs with differential, including platelet count, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

Table 3

Dose Adjustments of Eltrombopag in Adults with Refractory SAA (Promacta)	
Platelet Count Result	**Dose Adjustment or Response**

<50,000 following at least 2 weeks of eltrombopag	Increase daily dose by 36 mg to a maximum of 108 mg/day For persons taking 18 mg once daily; increase the dose to 36 mg daily before increasing the dose amount by 36 mg.
≥200,000 to ≤400,000 at any time	Decrease the daily dose by 36 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000	Stop eltrombopag for 1 week. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 36 mg.
>400,000 after 2 weeks of therapy at lowest dose of eltrombopag	Discontinue eltrombopag

- For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50%. If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to less than 30,000, hemoglobin to less than 9 g/dL, or ANC to less than 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.
- Discontinue eltrombopag if no hematologic response has occurred after 16 weeks of therapy. If new cytogenetic abnormalities are observed, consider discontinuation of eltrombopag. Excessive platelet count responses, as outlined in Table 3, or important liver test abnormalities also necessitate discontinuation of eltrombopag.

Drug Availability: Eltrombopag is supplied as a tablet in the following strengths:

Promacta: 12.5 mg, 25 mg, 50 mg, 75 mg tablets, and is also available as a 12.5 mg and 25 mg packet for oral suspension.

Alvaiz: 9 mg, 18 mg, 36 mg, and 54 mg tablets

PRECAUTIONS:

Boxed Warning:

Eltrombopag may cause hepatic decompensation in patients with chronic hepatitis C and risk of hepatotoxicity. When used in combination with interferon and ribavirin in persons with chronic HCV infection, eltrombopag may increase the risk of hepatic decompensation. The risk of severe and potentially life-threatening hepatotoxicity is increased with eltrombopag. Monitor hepatic function and discontinue dosing as recommended.

- Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation.
- Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.
- Discontinue eltrombopag if ALT levels increase to ≥3X upper limit of normal (ULN) in persons with normal liver function or ≥3X (or greater than 5 x ULN, whichever is lower) baseline in persons with pre-treatment elevations in transaminases and are:

- progressively increasing, or

- persistent for ≥4 weeks, or

- accompanied by increased direct bilirubin, or

- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Warnings/Precautions:

Hepatotoxicity: monitor liver function before and during therapy.

Hepatic decompensation: hepatic decompensation can occur in persons with chronic hepatitis C infection. Monitor persons with low albumin levels or with a MELD score of 10 or greater at baseline.

Increased risk of death and progression of Myelodysplastic Syndromes (MDS) to Acute Myeloid Leukemia (AML): A trial in patients with IPSS intermediate-1, intermediate-2 or high risk MDS with thrombocytopenia with azacitidine in combination with either eltrombopag or placebo was terminated due to lack of efficacy and safety.

Thrombotic/thromboembolic complications: portal vein thrombosis has been reported in persons with chronic liver disease receiving eltrombopag. Monitor platelet counts regularly.

Cataracts: monitor patients regularly for signs and symptoms of cataracts developing or worsening.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity:

B18.2	Chronic Viral Hepatitis C
C93.10	Chronic myelomonocytic leukemia
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20 – D46.21	Refractory anemia with excess of blasts
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.Z	Other myelodysplastic syndromes
D61.09	Other constitutional aplastic anemia
D61.1	Drug-induced aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.3	Idiopathic aplastic anemia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes

D61.9	Aplastic anemia, unspecified
D69.3	Immune thrombocytopenic purpura

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

International Prognostic Scoring System (IPSS): classification system used in staging individuals with MDS. The IPSS evaluates three components when determining an overall score of 0 to 2.5: percent marrow blasts, cytogenics (e.g., del(5)q chromosome), and cytopenias. An IPSS score of 0 corresponds to low risk, 0.5-1 to intermediate risk 1, 1.5-2 to intermediate risk 2, and 2.5 or greater to high risk.

IPSS Classification System	
Risk Level	IPSS Score
Low risk	0
Intermediate risk 1	0.5-1
Intermediate risk 2	1.5-2
High risk	2.5 or greater

The following factors are used to calculate the IPSS score

	0	0.5	1.0	1.5	2.0
% Marrow Blasts	Less than 5	5-10		11-20	21-30
Cytogenetics	Normal, -Y, del(5)g alone, del(20)q alone	Other	-7, del (7)q, 3 or more abnormalities		
Cytopenias • Hemoglobin <10 g/dL Neutrophil count less than 1800/mcL • Platelet count less than 100,000 cells/mm3	Only 1	Two of the three			
ANC, absolute neutrophil count					

Myelodysplastic Syndrome (MDS): any of a group of related bone marrow disorders of varying duration preceding the development of overt acute myelogenous leukemia; they are characterized by abnormal hematopoietic stem cells, anemia, neutropenia and thrombocytopenia. Also called releukemia.

Revised International Prognostic Scoring System (IPSS-R): classification system used in staging individuals with MDS. Individuals are assigned to 1 of 5 risk groups.

IPSS-R Classification System	
Risk Level	IPSS-R Score
Very Low	≤1.5
Low	>1.5- ≤3
Intermediate	>3 - ≤4.5
High	>4.5 - ≤6
Very High	>6

The following factors are used to calculate the IPSS-R score

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
% Marrow Blasts	≤2	-	>2 - <5	-	5-10	>10	-
Hemoglobin	≥10	-	8 - <10	< 8			
Platelets	≥100	50 - <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-
ANC, absolute neutrophil count							

Thrombocytopenic Purpura: any of various types associated with a decrease in the number of platelets in the blood; there are two general types: in the primary or idiopathic type, the cause is unknown. The secondary or symptomatic type may be associated with exposure to drugs or other chemical agents or with any of numerous different diseases. The most prominent symptoms are bruising and petechiae. In the acute form there may be bleeding from body orifices.

World Health Organization (WHO) Prognostic Scoring System (WPSS): classification system used in staging individuals with MDS. This system is based on the WHO classification of the MDS subtype, karyotype, and presence of severe anemia. Individuals are assigned to 1 of 5 risk groups and the risk category may change over the course of the disease.

WPSS Classification System				
	Score			
Variable	0	1	2	3
WHO Category	RCUD, RARS, MDS with isolated del (5q)	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	--
Severe anemia (hemoglobin <9 g/dL in males or <8 g/dL in females)	Absent	Present	--	--

RCUD, refractory cytopenia with unilineage dysplasia (includes refractory anemia, refractory neutropenia, and refractory thrombocytopenia); RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; A score of 0=very low risk, 1= low risk, 2=intermediate risk, 3-4=high risk, 5-6=very high risk

RELATED GUIDELINES:

Avatrombopag (Doptelet®), 09-J3000-02
Fostamatinib (Tavalisse), 09-J3000-00
Hepatitis C Drug Therapy, 09-J0000-53
Immune Globulin Therapy, 09-J0000-06
Rituximab (Rituxan®), 09-J0000-59
Romiplostim Injection (Nplate™), 09-J0000-88

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/13/24.

GUIDELINE UPDATE INFORMATION:

11/15/09	New Medical Coverage Guideline.
07/15/10	Review and revision to guideline; consisting of adding criteria of absence of chronic liver disease, updated precautions and references.
01/15/11	Revision to guideline; consisting of adding ICD-10 codes.
07/15/11	Review and revision to guideline; consisting of updating dosing, precautions and references.
03/15/12	Revision to guideline; consisting of removing requirement for REMS enrollment.
07/15/12	Review and revision to guideline; consisting of updating position statement and references.
02/15/13	Update to include new indication thrombocytopenia in HCV therapy, updated to include continuation of therapy for ITP and thrombocytopenia in HCV therapy
07/15/13	Review and revision to guideline; consisting of revising/reformatting position statement; revising/ reformatting description, dosage/administration, program exceptions and precautions section; updating references.
07/15/14	Review and revision to guideline; consisting of revising and reformatting the position statement. Updated dosage/administration section and references.
7/15/15	Review and revision to guidelines; consisting of revising and reformatting the position statement, description, dosage/administration, precautions and references section.
10/15/15	Revision to guideline; consisting of position statement
11/01/15	Revision: ICD-9 Codes deleted.
07/15/16	Review and revision to guidelines; consisting of updating the position statement, description, dosing, coding and references section.
09/15/19	Review and revision to guidelines; consisting of updating the position statement, dosing, and references section.
12/15/19	Review and revision to guidelines; consisting of updating the position statement, description, coding and references.
07/15/20	Revision to guideline; consisting of updating the position statement and references.

12/15/21	Review and revision to guideline; consisting of updating the position statement and references.
12/15/22	Review and revision to guideline; consisting of updating documentation of improvement of platelet count under continuation criteria and updating use for myelodysplastic syndrome. Updated references.
12/15/23	Review and revision to guideline; consisting of updating the position statement to include thrombocytopenia following hematopoietic cell transplant and references.
01/15/25	Review and revision to guideline; consisting of updating MCG to include Alvaiz and included risk of bleeding for Promacta.