

## Policy Type: PA/SP

## Pharmacy Coverage Policy: EOCCO169

### Description

Avatrombopag (Doptelet®), eltrombopag olamine (Promacta®), eltrombopag choline (Alvaiz®), lusutrombopag (Mulpleta®) are thrombopoietin (TPO) receptor agonists that induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation, thus resulting in an increased production of platelets.

Fostamatinib (Tavalisse™) is a tyrosine kinase inhibitor (TKI) with activity against spleen tyrosine kinase (SYK). Fostamatinib metabolite, R406, inhibits signal transduction of Fc-activating receptors, B-cell receptors, and reduces antibody-mediated destruction of platelets.

### Length of Authorization

- Initial:
  - **Avatrombopag (Doptelet)**
    - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
    - Chronic immune thrombocytopenia (ITP): Three months
  - **Eltrombopag olamine (generic and brand Promacta)**
    - Chronic thrombocytopenia due to chronic hepatitis C: three months
    - Chronic Immune Thrombocytopenia (ITP): three months
    - First-line treatment severe aplastic anemia: six months
    - Severe aplastic anemia, refractory: four months
  - **Eltrombopag choline (Alvaiz)**
    - Chronic thrombocytopenia due to chronic hepatitis C: three months
    - Persistent or Chronic thrombocytopenia (ITP): Three months
    - Severe aplastic anemia, refractory: four months
  - **Lusutrombopag (Mulpleta)**
    - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
  - **Fostamatinib (Tavalisse)**
    - Chronic Immune Thrombocytopenia (ITP): three months
- Renewal:
  - i. **Avatrombopag (Doptelet), eltrombopag olamine (generic and brand Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse)**
    - Chronic Immune Thrombocytopenia (ITP), refractory severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C: six months

## Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
avatrombopag (Doptelet)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	20 mg tablet	15 tablets/ 30 days
	Chronic Immune Thrombocytopenia (ITP)		60 tablets/30 days
eltrombopag olamine (generic and brand Promacta)	Severe aplastic anemia	12.5 mg/1 packet	<b>[2 to 5 Years of age]</b> 2.5mg/kg/day <b>[6 to 11 Years of age]</b> 30 packets/30 days (3 kits/30 days) <b>[12 years and older]</b> 30 packets/30 days (6 kits/30 days)
		25 mg/1 packet	<b>[2 to 5 Years of age]</b> 2.5mg/kg/day <b>[6 to 11 Years of age]</b> 90 packets/30 days (3 kits/30 days) <b>[12 years and older]</b> 180 packets/30 days (6 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	30 tablets/ 30 days
		75 mg tablet	60 tablets/ 30 days
	Chronic thrombocytopenia due to chronic Hepatitis C	12.5 mg/1 packet	30 packets/ 30 days (4 kits/30 days)
		25 mg/1 packet	120 packets/30 days (4 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	60 tablets/ 30 days
		75 mg tablet	30 tablets/ 30 days
	Persistent or Chronic immune thrombocytopenia (ITP)	12.5 mg/1 packet	30 packets/30 days (3 kits/30 days)
		25 mg/1 packet	90 packets/30 days (3 kits/30 days)
		12.5 mg tablet	

		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	
		75 mg tablet	
lusutrombopag (Mulpleta)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	3 mg tablet	7 tablets/ 365 days
fostamatinib (Tavalisse)	Chronic Immune Thrombocytopenia	100 mg tablets	60 tablets/30 days
		150 mg tablets	
eltrombopag Choline (Alvaiz)	Persistent or Chronic Immune Thrombocytopenia	9 mg tablet	30 tablets/30 days
		18 mg tablet	30 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Chronic Hepatitis C Thrombocytopenia	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Severe Aplastic Anemia (refractory)	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	60 tablets/30 days
		54 mg tablet	60 tablets/30 days

## Initial Evaluation

- I. **Avatrombopag (Doptelet), generic eltrombopag olamine, eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta) and fostamatinib (Tavalisse)** may be considered medically necessary when the following criteria below are met:
  - A. Medication is prescribed by, or in consultation with, a hematologist or gastroenterologist; **AND**
  - B. Medication is not used in combination with another thrombopoietin (TPO) receptor agonists (e.g. avatrombopag, eltrombopag, lusutrombopag); **AND**
  - C. A diagnosis of one of the following:
    1. **Chronic liver disease (CLD)-associated thrombocytopenia; AND**
      - i. Member is 18 years of age or older; **AND**
      - ii. Member has a platelet count less than  $50 \times 10^9/L$ ; **AND**
      - iii. Request is for avatrombopag (Doptelet) OR lusutrombopag (Mulpleta); **AND**
        - a. Member is scheduled to undergo an invasive procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, or liver biopsy); **OR**

- iv. Member has a diagnosis of **chronic Hepatitis C infection**; **AND**
  - a. Member is unable to initiate or maintain interferon-based treatment [eg. pegylated interferon (Pegasys®) and ribavirin]; **AND**
  - b. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
  - c. Request is for brand eltrombopag olamine (Promacta); **AND**
    - i. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated; **OR**
- 2. **Persistent or Chronic Immune Thrombocytopenia; AND**
  - i. Treatment with first-line therapies (e.g corticosteroids, immunoglobulins, or splenectomy) have been ineffective, contraindicated, or not tolerated; **AND**
  - ii. Member has a platelet count that is less than 30 x 10<sup>9</sup>/L with symptoms of bleeding; **AND**
  - iii. Member is one year of age or older; **AND**
    - a. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
    - b. Request is for brand eltrombopag olamine (Promacta); **AND**
      - i. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated); **OR**
  - iv. Member is 18 years of age or older; **AND**
    - a. Request is for avatrombopag (Doptelet); **OR**
    - b. Request is for fostamatinib (Tavalisse); **OR**
- i. **Severe aplastic anemia; AND**
  - i. Member has met at least two of the following three criteria:
    - 1. Absolute neutrophil count (ANC) less than 500/microL; **OR**
    - 2. Platelet count less than 20,000/microL; **OR**
    - 3. Absolute reticulocyte count (ARC) less than 60,000/microL; **AND**
  - ii. Member has **NOT** received prior immunosuppressive therapy (IST) (e.g., request as first-line); **AND**
    - a. Member is two years of age or older; **AND**
    - b. Treatment will be initiated concurrently with immunosuppressive therapy (e.g., horse antithymocyte globulin (h-ATG) and cyclosporine); **AND**
    - c. The request is for generic eltrombopag olamine; **OR**
    - d. The request is for brand eltrombopag olamine (Promacta); **AND**

- a. Generic eltrombopag olamine has been ineffective, not tolerated, or contraindicated; **OR**
- iii. Member has severe aplastic anemia with refractory thrombocytopenia; **AND**
  - a. Treatment with at least one course of horse or rabbit anti-thymocyte globulin (ATG) and cyclosporine A (CSA) has been ineffective, contraindicated or not tolerated; **AND**
  - b. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
  - c. Request is for brand eltrombopag olamine (Promacta); **AND**
    - a. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated
- II. Avatrombopag (Doptelet) is considered investigational when used for all other conditions, including but not limited to:
  - A. Chemotherapy-induced thrombocytopenia in adults with active non-hematological cancers
- III. Eltrombopag olamine (Promacta) is considered investigational when used for all other conditions, including but not limited to:
  - A. Elderly patients with Acute Myeloid Leukemia receiving induction chemotherapy
  - B. Prevention of chemotherapy induced thrombocytopenia
  - C. Thrombocytopenia with chronic HBV infection
  - D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
  - E. Thrombocytopenia associated with myelodysplastic syndrome
- IV. Eltrombopag choline (Alvaiz) is considered investigational when used for all other conditions, including but not limited to:
  - A. Myelodysplastic syndromes: thrombocytopenia, monotherapy in adult patients
  - B. Acute Myeloid Leukemia in adults
- V. Lusutrombopag (Mulpleta) is considered investigational when used for all other conditions.
- VI. Fostamatinib (Tavalisse) is considered investigational when used for all other conditions, including but not limited to:
  - A. Malignancies:
    - 1. Advanced colorectal, non-small cell lung, head and neck hepatocellular and renal cell carcinomas, and pheochromocytoma and thyroid tumors
    - 2. B-cell Lymphoma
    - 3. Large B-Cell Lymphoma

- 4. Ovarian Cancer
- 5. T-Cell Lymphoma
- B. Rheumatoid Arthritis (RA)
- C. Renal Transplant Rejection (antibody mediated rejection)
- D. Chronic Graft vs. Host Disease

### Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
  - A. **Chronic thrombocytopenia due to chronic Hepatitis C; AND**
    - 1. Member is unable to initiate or maintain interferon-based treatment [e.g. pegylated interferon (Pegasys®) and ribavirin]; **OR**
  - B. **Persistent or Chronic Immune Thrombocytopenia; AND**
    - 1. Platelet count has increased to greater than or equal to 50 x10<sup>9</sup>/L; **OR**
  - C. **Severe aplastic anemia; AND**
    - 1. Absolute neutrophil count (ANC) less than 500/microL at baseline; **AND**
      - i. ANC has increased 100%; **OR**
      - ii. An ANC increase greater than or equal to 500/microL; **OR**
    - 2. Platelet count was less than 20,000/microL at baseline; **AND**
      - i. Increase in platelet count has been greater than or equal to 20,000/microL from baseline; **OR**
      - ii. Stable platelet counts with transfusion independence for ≥ 8 weeks; **OR**
    - 3. Absolute reticulocyte count (ARC) less than 60,000/microL at baseline; **AND**
      - i. There has been an increase in hemoglobin by 1.5 g/dL; **OR**
      - ii. In patients receiving transfusions, there has been a reduction in red blood cell transfusions; **AND**
- IV. If the request is for brand eltrombopag olamine (Promacta): Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated

### Supporting Evidence

- I. The clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta), and fostamatinib (Tavalisse) did not include patients who were concomitantly using another TPO receptor agonists. Due to this, there is no data to assess the safety and efficacy of these agents when used concomitantly.



- II. Considering the complexity of the indications and agents, they must be prescribed by, or in consultation with, a hematologist or gastroenterologist.
- III. The safety and efficacy clinical trials of avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta) for chronic liver disease (CLD)-associated thrombocytopenia, did not include patients younger than 18 years of age. Therefore, there is no clinical trial data to support the use of these agents in pediatric patients.
- IV. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta), for chronic liver disease (CLD)-associated thrombocytopenia, were studied in patients with a platelet count less than  $50 \times 10^9/L$ . This is because the risk for serious bleeding does not occur until the platelet count becomes very low—less than  $10 \times 10^9/L$  or  $20 \times 10^9/L$ , with the risk for mild bleeding occurring when the platelet count is less than  $50 \times 10^9/L$ . These agents should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from  $150 \times 10^9/L$  to  $450 \times 10^9/L$ ).
- V. Avatrombopag (Doptelet) and lusutrombopag (Mulpleta) are indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, liver biopsy). They should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from  $150 \times 10^9/L$  to  $450 \times 10^9/L$ ).
- VI. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) are indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It 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. It should not be used to normalize platelet counts outside of this indication (normal platelet count in adults ranges from  $150 \times 10^9/L$  to  $450 \times 10^9/L$ ).
- VII. There is no safety and efficacy data to show superiority of one formulation over the other. The effectiveness of eltrombopag choline (Alvaiz) has been established based on adequate and well-controlled studies of eltrombopag olamine (Promacta) in adult and pediatric patients 6 years and older with persistent or chronic ITP, adult patients with chronic hepatitis C-associated thrombocytopenia, and adults patients with severe refractory aplastic anemia. In November 2023, Alvaiz was approved under the FDA accelerated approval 505(b)(2) process. The fundamental differences between the two salt forms: choline and olamine, respectively are the cost-effectiveness, dosage formulations, and differences of indications in both adult and patient populations. Eltrombopag choline (Alvaiz) has a reduced food effect therefore influencing the overall bioavailability for a patient in comparison to Eltrombopag olamine (Promacta). Per the

package insert Alvaiz cannot be substituted with another eltrombopag product on a milligrams per milligrams basis. Although Alvaiz has reduced food effect, and therefore slightly increased bioavailability, the overall therapeutic effect remains similar to Promacta. This is reinforced by the package insert guidance to retain the same strict reduction of calcium intake (<50mg) and to refrain from administering Alvaiz 2 hours prior to and/or 4 hours post consumption of calcium and/or supplements containing polyvalent cations.

- VIII. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) are indicated for the treatment of patients with chronic immune thrombocytopenia who have had an insufficient response to a first-line treatment (e.g. corticosteroids, immunoglobulins, or splenectomy).
- IX. According to American Society of Hematology 2019 clinical guidelines thrombopoietin receptor agonists such as Eltrombopag olamine (Promacta) are considered second line therapy for management of immune thrombocytopenia.
- X. Patients with platelet counts less than  $30 \times 10^9/L$  were included in clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse).
- XI. The efficacy and safety of eltrombopag olamine (Promacta) in pediatric patients one year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. The primary endpoint was participants who achieved a platelet count greater than, or equal to,  $50 \times 10^9/L$  for at least six out of eight weeks, generally seen between weeks five and 12. Pediatric patients (75%) treated with eltrombopag olamine (Promacta), compared with placebo (21%), saw an increased value with at least one platelet count greater than, or equal to,  $50 \times 10^9/L$  during the first 12 weeks of randomized treatment in absence of rescue therapy. Platelet response to eltrombopag olamine (Promacta) was consistent across the age cohorts. Fewer pediatric patients treated required rescue treatment during the randomized, double blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).
  - a. The safety and effectiveness of eltrombopag choline (Alvaiz) has not been established in pediatric patients less than 6 years of age with persistent or chronic ITP. Pediatric patients must be able to swallow eltrombopag choline (Alvaiz) tablets whole.
- XII. The safety and efficacy clinical trials of avatrombopag (Doptelet) and fostamatinib (Tavalisse), for chronic ITP, did not include patients younger than 18 years of age.
  - o Fostamatinib (Tavalisse) is not recommended for use in patients less than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies. In subchronic, chronic, and carcinogenicity studies, chondrodystrophy of the femoral head was seen in rodents.
- XIII. Eltrombopag olamine (Promacta) is indicated in combination with standard immunosuppressive therapy for the first-line treatment of severe aplastic anemia and of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.



Eltrombopag choline (Alvaiz) does not share this indication with eltrombopag olamine (Promacta).

- XIV. According to aplastic anemia & MDS international foundation (AAMDS) for a confirmed diagnosis of aplastic anemia the patient has to have met at least two of the following cell counts: absolute neutrophil count (ANC) less than 500/microL, platelet count less than 20,000/microL, or absolute reticulocyte count (ARC) less than 60,000/microL.
- XV. Thirty-four patients, two to 16 years of age, were enrolled in Study US01T. The primary outcome was rate of complete hematologic response at six months. In the D1-M6 cohort, 7 and 17 out of 25 pediatric patients achieved a complete and overall response, respectively, at six months.
- XVI. Ninety-two patients were enrolled in a prospective phase 1-2 study of immunosuppressive therapy plus eltrombopag olamine (Promacta). The three consecutively enrolled cohorts differed regarding the timing of initiation and the duration of the eltrombopag olamine (Promacta) regimen (cohort 1 received eltrombopag olamine (Promacta) from day 14 to six months, cohort 2 from day 14 to three months, and cohort 3 from day one to six months). The primary outcome was complete hematologic response at 6 months. Secondary end points included overall response, survival, relapse, and clonal evolution to myeloid cancer. The rate of complete response at 6 months was 33% in cohort 1, 26% in cohort 2, and 58% in cohort 3. The overall response rates at 6 months was 80% cohort 1, 87% cohort 2, and 94% cohort 3. The addition of eltrombopag olamine (Promacta) to immunosuppressive therapy (e.g. horse antithymocyte globulin (h-ATG) and cyclosporine) was associated with higher rates of hematologic response among patients with severe aplastic anemia than in a historical cohort.
- XVII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy.
- XVIII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It 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. It should not be used to normalize platelet counts (normal platelet count in adults ranges from  $150 \times 10^9/L$  to  $450 \times 10^9/L$ ).
- XIX. Treatment with avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) should be discontinued after 12 weeks (three months) of treatment if platelet counts do not increase to a level sufficient to avoid clinically important bleeding (greater than or equal to  $50 \times 10^9/L$  – risk for serious bleeding doesn't occur until the count becomes very low—less than  $10 \times 10^9/L$  or  $20 \times 10^9/L$ , and for mild bleeding when the count is less than  $50 \times 10^9/L$ ). These agents should not be administered to patients with chronic liver disease, that do not meet this criterion, in an effort to normalize platelet counts (normal platelet count in adults ranges from  $150 \times 10^9/L$  to  $450 \times 10^9/L$ ).

- XX. In the clinical trial, the primary end point was hematologic response at three to four months and defined as uni- or multilineage recovery by one or more of the following criteria: (1) platelet response (increase to  $20 \times 10^3/\mu\text{L}$  above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks in those who were transfusion dependent on entry into the protocol); (2) erythroid response (when pretreatment hemoglobin was  $<9 \text{ g/dL}$ , defined as an increase in hemoglobin by  $1.5 \text{ g/dL}$  or, in transfused patients, a reduction in the units of packed red blood cell transfusions by an absolute number of at least 4 transfusions for 8 consecutive weeks, compared with the pretreatment transfusion number in the previous 8 weeks); and (3) neutrophil response (when pretreatment absolute neutrophil count [ANC] of  $<0.5 \times 10^3/\mu\text{L}$  as at least a 100% increase in ANC, or an ANC increase  $>0.5 \times 10^3/\mu\text{L}$ , and the toxicity profile as measured using Common Terminology Criteria for Adverse Events).
- XXI. Generic formulations of eltrombopag olamine (both tablets and oral suspension) are now commercially available for treating thrombocytopenia associated with chronic hepatitis C, severe aplastic anemia, and immune thrombocytopenia. Requiring treatment with generic eltrombopag olamine or eltrombopag choline (Alvaiz) prior to approval of brand eltrombopag olamine (Promacta) is clinically appropriate and cost-effective.

### Investigational or Not Medically Necessary Uses

- I. Avatrombopag (Doptelet)
  - A. Chemotherapy-Induced Thrombocytopenia in adults with active non-hematological cancers
    - i. A randomized, double-blind, placebo-controlled study with an open-label extension to evaluate the efficacy and safety of avatrombopag (Doptelet) for the treatment of chemotherapy-induced thrombocytopenia in subjects with active non-hematological cancers is still recruiting.
  - B. There is limited or no published clinical trial data to support the use of avatrombopag (Doptelet) in conditions other than thrombocytopenia associated with chronic liver disease prior to planned procedure and chronic immune thrombocytopenia (ITP).
- II. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz)
  - A. Elderly Patients with Acute Myeloid Leukemia receiving induction chemotherapy (EPAG2015)
    - i. A Phase II, randomized, placebo-controlled study to assess the impact on outcome of eltrombopag (Promacta) administered to elderly patients with acute myeloid leukemia receiving induction chemotherapy in 110 participants and is still recruiting.
  - B. Prevention of chemotherapy induced thrombocytopenia
    - i. A phase I/II open-label study of eltrombopag for the prevention of chemotherapy induced thrombocytopenia (CIT) in subjects with advanced soft tissue and bone sarcomas receiving gemcitabine and docetaxel chemotherapy was terminated.
  - C. Thrombocytopenia with chronic HBV infection

- i. A multicenter, single-arm, open-label study in 58 participants to evaluate the efficacy and safety of eltrombopag for thrombocytopenia in Chinese patients with chronic HBV infection is still recruiting.
- D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
  - i. Randomized, single arm, single-blind study in 220 participants of eltrombopag (Promacta) and eltrombopag choline (Alvaiz) in thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML) is in recruiting stage.
- E. Thrombocytopenia associated with myelodysplastic syndrome
  - i. In a three-part study of eltrombopag in thrombocytopenic subjects with myelodysplastic syndromes or acute myeloid leukemia.
    - 1. Part 1 was an open-label with 17 patients receiving eltrombopag and 11 patients completing treatment. Primary endpoint was number of participants with platelet response up to week 8 and four experienced significantly increased platelet counts, and ten had reduced platelet transfusion requirements.
    - 2. Part 2 was a randomized, double-blind with 145 patients who received supportive care plus eltrombopag (n=98) or placebo (n=47). Primary outcome was clinically relevant thrombocytopenic events (CRTE) from week 5 up to week 12. Average weekly CRTE were significantly lower with eltrombopag (54% [95% CI 43-64]) than with placebo (69% [57-80], odds ratio [OR] 0.20, 95% CI 0.05-0.87; p=0.032) although the difference between treatment groups was less than 30%. Serious adverse events were reported in 56 (58%) eltrombopag-treated patients and 32 (68%) placebo-treated patients. Seven eltrombopag recipients and two placebo recipients had serious adverse events that were suspected to be study drug-related (acute kidney injury, arterial thrombosis, bone pain, diarrhea, myocardial infarction, pyrexia, retinal vein occlusion, n=1 each; placebo: vomiting, white blood cell count increased, n=1 each). Two eltrombopag recipients had arterial thrombosis n=1 and myocardial infarction n=1. No placebo recipients experienced fatal or serious adverse events suspected to be study drug related.
    - 3. Part 3 is an extension ongoing study.
    - 4. Overall the clinical trial had a small patient population, showed limited efficacy and had questionable safety.
  - ii. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukemia was completed in a multicenter, randomized, placebo-controlled, double-blind, phase 1/2 trial.

1. Primary outcome was safety and tolerability parameters including non-hematological laboratory Grade 3/Grade 4 toxicities, change in bone marrow blast counts from baseline, and adverse events reporting. [ Time Frame: Approximately 46 months].
  2. Ninety-eight patients were randomized to receive either eltrombopag (n=64) or placebo (n=34). Sixty-three (98%) patients in the eltrombopag group and 32 (94%) patients in the placebo group had adverse events. The most common adverse events were pyrexia (27 [42%] vs 11 [32%]), nausea (20 [31%] vs 7 [21%]), diarrhea (19 [30%] vs 6 [18%]), fatigue (16 [25%] vs 6 [18%]), decreased appetite (15 [23%] vs 5 [15%]), and pneumonia (14 [22%] vs 8 [24%]). Drug-related adverse events of grade 3 or higher were reported in six (9%) patients in the eltrombopag group and four (12%) patients in the placebo group.
  3. In this clinical trial efficacy was not assessed.
- F. There is limited or no published clinical trial data to support the use of eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) in conditions other than severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C, and chronic immune thrombocytopenia (ITP).
- III. Lusutrombopag (Mulpleta)
- A. There is limited or no published clinical trial data to support the use of lusutrombopag (Mulpleta) in conditions other than thrombocytopenia associated with chronic liver disease prior to a planned procedure.
- IV. Fostamatinib (Tavalisse)
- A. Malignancies
- i. Advanced colorectal, non-small cell lung, head, and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors
    1. A broad, multi-histology, single group assignment, open label, phase II study of the multi-kinase inhibitor R935788 (fostamatinib disodium) in advanced colorectal, non-small cell lung, head and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors in 37 participants.
    2. Fostamatinib had limited anti-tumor activity in this first clinical trial in patients with advanced refractory solid tumors; reduction in CECs and CEPs was indicative of anti-angiogenic effects. Abnormal liver testing at baseline appeared to influence drug tolerability.
- B. B-cell Lymphoma
- i. A Phase I/II, multi-Center, single group assignment, open label trial of the safety and efficacy of fostamatinib in 81 patients with relapsed/refractory B-cell lymphoma. The clinical trial showed limited efficacy and considering it is an open

label, single group trial, further clinical research is necessary to show efficacy and safety.

- C. Large B-cell lymphoma, relapsed or refractory
  - i. Phase II, single group assignment, open label trial with 101 participants to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The clinical trial showed limited efficacy and considering it is an open label, single group trial, further clinical research is necessary to show efficacy and safety.
- D. Ovarian cancer
  - i. Phase I, single group assignment, open label clinical trial of combined fostamatinib and paclitaxel in ovarian cancer with 18 participants and still recruiting.
- E. T-cell lymphoma
  - i. Phase II, multicenter, open label, single assessment group, simon two-stage study of fostamatinib disodium in patients with relapsed or refractory T-cell lymphoma in 18 participants. The clinical trial was not blinded or randomized. It wasn't powered enough to show efficacy or safety of fostamatinib (Tavalisse) in T-cell lymphoma.
- F. Rheumatoid arthritis (RA)
  - i. A Long-term, open label, single assignment study to assess the safety of fostamatinib in the treatment of rheumatoid arthritis in Asia was terminated.
  - ii. A Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of two dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor- $\alpha$  antagonist.
  - iii. Adult patients were randomized (1:1:1) to fostamatinib [100 mg bid for 24 weeks (n=105; Group A)], or 100 mg bid for 4 weeks, then 150 mg qd (n=108; Group B), or to placebo (n=110; Group C) for 24 weeks. Nonresponders at Week 12 could enter a long-term extension study. The primary endpoint was the proportion of patients achieving an American College of Rheumatology 20% (ACR20) response at Week 24.
  - iv. Due to efficacy and safety results from the clinical trial, the companies developing fostamatinib have decided not to study it further in RA at this time.
- G. Renal Transplant Rejection (antibody mediated rejection)
  - i. Fostamatinib is being studied in a phase 2, single center, not randomized, open label, pilot study to assess the safety and efficacy of fostamatinib in the treatment of chronic active antibody mediated rejection in renal transplantation is still recruiting.
- H. Chronic Graft vs. Host Disease

- i. A phase I, open label, single group assignment trial of fostamatinib and chronic graft vs. host disease development after allogeneic stem cell transplantation with 18 participants is still recruiting.
- I. There is limited or no published clinical trial data to support the use of fostamatinib (Tavalisse) in conditions other than chronic immune thrombocytopenia (ITP).

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### Policy Implementation/Update

Action and Summary of Changes	Date
Updated policy name to “Thrombopoietic Agents” policy. Updated initial and renewal policy criteria to include trial of generic eltrombopag olamine or eltrombopag choline (Alvaiz) prior to brand Promacta.	06/2025
Added coverage of persistent immune thrombocytopenia for eltrombopag olamine (Promacta). Removed requirement to trial oral Promacta tablets prior to Promacta packets.	05/2024
Added eltrombopag choline (Alvaiz) for the treatment of persistent or chronic immune thrombocytopenia in adult and pediatric patients 6 years of age and older, chronic Hepatitis C-associated thrombocytopenia, and severe aplastic anemia (refractory). Updated supporting evidence, references, and formatting.	03/2024
Added new strength of 25mg eltrombopag (Promacta) packet for oral suspension	05/2020

<ul style="list-style-type: none"> <li>Added investigational indications for avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)</li> <li>Added age limits to eltrombopag (Promacta) for immunosuppressive naive Severe aplastic anemia at two years of age or older, and relapsed or refractory severe aplastic anemia at 18 years of age or older.</li> <li>Added criteria for Severe aplastic anemia; [Member has to meet at least two of the following three criteria are met: 1) Absolute neutrophil count (ANC) less than 500/microL, or 2) Platelet count less than 20,000/microL, or 3) Absolute reticulocyte count (ARC) less than 60,000/microL</li> <li>Added member is 18 years of age or older if request is for avatrombopag (Doptelet), fostamatinib (Tavalisse) and fostamatinib (Tavalisse) [for chronic ITP]</li> <li>Added criteria if request is for eltrombopag (Promacta) packets, member has demonstrated inability to swallow tablets</li> <li>Changed QL for eltrombopag (Promacta) packets</li> <li>Changed QL for avatrombopag (Doptelet) for chronic immune thrombocytopenia (ITP)</li> <li>Changed initial and renewal length of authorization for all agents</li> <li>Combined as one policy: avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) with fostamatinib (Tavalisse)</li> </ul>	02/2020
Previous reviews fostamatinib (Tavalisse)	06/2018, 11/2019,
Conversion to policy format fostamatinib (Tavalisse)	11/2019
Avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) combined as policy: TPO-Receptor Agonists	10/2019
Previous reviews avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019,
Policy created avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019
Policy created fostamatinib (Tavalisse)	06/2018