BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ALVAIZ™ (eltrombopag) oral
DOPTELET® (avatrombopag) oral
MULPLETA® (lusutrombopag) oral
PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

Section A. Thrombocytopenia from Severe Aplastic Anemia:
ALVAIZ (eltrombopag)
PROMACTA (eltrombopag)

- **Criteria for initial therapy:** Alvaiz (eltrombopag), Promacta (eltrombopag), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

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1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with Hematologist or Transplantation Specialist (when appropriate)

2. Individual has a confirmed diagnosis of ***thrombocytopenia from severe aplastic anemia*** and is **ONE** of the following:
    a. **For Promacta**: First-line treatment of individual 2 years of age or older with severe aplastic anemia used in combination with standard immunosuppressive therapy
    b. **For Alvaiz or Promacta**: Individual 18 years of age or older who had an insufficient response to immunosuppressive therapy defined as failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following:
        i. Antithymocyte globulin [Thymoglobulin, Atgam] with cyclosporine with or without a corticosteroid
        ii. Antithymocyte globulin with cyclophosphamide with or without a corticosteroid

3. Individual does not have myelodysplastic syndrome (MDS)

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. The degree of thrombocytopenia and clinical condition increases the risk for bleeding **OR** has documented bleeding symptoms

6. Individual has severe aplastic anemia with at least **TWO** of the following:
    a. Platelet count is less than 20 x 10^9/L
    b. Reticulocyte count is less than 50 x 10^9/L
    c. Absolute neutrophil count is less than 0.5 x 10^9

7. Will not be used to normalize platelet count

8. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Complete blood count
    b. Liver function tests
    c. Ocular examination for detection of cataracts

9. Will not be used in combination with Doptelet (avatrombopag), Mulpleta (lusutrombopag), Tavalisse (fostamatinib), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

Initial approval duration: 6 months

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Generic Equivalent (if available)

- **Criteria for continuation of coverage (renewal request):** Alvaiz (eltrombopag), Promacta (eltrombopag olamine), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in platelet disorders or is in consultation with a Hematologist or Transplantation Specialist (when appropriate)

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
   a. Achieved and maintains a stable platelet count **or** platelet count increased 20 x 10^9/L above baseline
   b. Hemoglobin increased by > 1.5 g/dL **or** a reduction in RBC infusion of ≥ 4 units
   c. Reticulocyte count is greater than 60 x 10^9/L
   d. ANC increase of 100% **or** an ANC increase > 0.5 x 10^9/L
   e. Has not had any serious or severe bleeding events requiring rescue with any of the following:
      i. Platelet transfusions, fresh frozen plasma, whole blood, packed red blood cells, cryoprecipitate, vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, surgical or interventional radiology procedure to control blood loss
   f. Has not had any hospitalizations for severe thrombocytopenia

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does not have myelodysplastic syndrome (MDS)

6. Will not be used to normalize platelet count and will not be used if the platelet count is greater than 400 x 10^9/L

7. Will not be used in combination with Doptelet (avatrombopag), Mulpleta (lusutrombopag), Tavalisse (fostamatinib), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

8. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Thrombotic/thromboembolic complications (such as DVT, PE, stroke, MI)
   b. Persistent platelet count >400 x 10^9/L
   c. Hyperbilirubinemia
   d. Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
   e. Development or worsening of cataracts
   f. Myelodysplastic syndrome
   g. Acute Myeloid Leukemia

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Section B. Chronic immune (idiopathic) thrombocytopenia (ITP): ALVAIZ (eltrombopag) DOPTELET (avatrombopag) PROMACTA (eltrombopag) TAVALISSE (fostamatinib)

- **Criteria for initial therapy:** Alvaiz (eltrombopag), Doptelet (avatrombopag), Promacta (eltrombopag), Tavalisse (fostamatinib), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in platelet disorders or is in consultation with Hematologist or Transplantation Specialist (when appropriate)

  2. Individual's age is **ONE** of the following:
     a. **For Alvaiz (eltrombopag):** 6 years of age or older
     b. **For Doptelet (avatrombopag):** 18 years of age or older
     c. **For Promacta (eltrombopag):** 1 year of age or older
     d. **For Tavalisse (fostamatinib):** 18 years of age or older

  3. Individual has a confirmed diagnosis of ***persistent or chronic immune (idiopathic) thrombocytopenia (ITP)***

  4. The degree of thrombocytopenia and clinical condition increases the risk for bleeding **OR** has documented bleeding symptoms

  5. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** the following:
     a. Corticosteroid
     b. Immunoglobulin
     c. Splenectomy **or** is not a candidate for splenectomy

6. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. **For Doptelet (avatrombopag):**
        i. Platelet count is less than 30 x 10^9/L or is between 30-50 x 10^9/L and has documented bleeding symptoms or an increased risk for bleeding
    b. **For Alvaiz (eltrombopag) or Promacta (eltrombopag):**
        i. Platelet count is less than 30 x 10^9/L or is between 30-50 x 10^9/L and has documented bleeding symptoms or an increased risk for bleeding
        ii. Complete blood count
        iii. Liver function tests
        iv. Ocular examination for detection of cataracts
    c. **For Tavalisse (fostamatinib):**
        i. Platelet count is less than 30 x 10^9/L or is between 30-50 x 10^9/L and has documented bleeding symptoms or an increased risk for bleeding
        ii. Complete blood count
        iii. Liver function tests
        iv. Blood pressure, if abnormal, antihypertensive medication(s) have been initiated or adjusted
        v. Negative pregnancy test in a woman of childbearing potential

8. Will not be used to normalize platelet count and will not be used if the platelet count is greater than 400 x 10^9/L

9. Will not be used in combination with each other or with Mulpleta (lusutrombopag), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

10. **Additional criteria for Alvaiz and Promacta**: Will not be used to treat individuals with myelodysplastic syndromes (MDS)

11. **Additional criteria for Tavalisse only:** Individual is not using strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, others

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Alvaiz (eltrombopag), Doptelet (avatrombopag), Promacta (eltrombopag), Tavalisse (fostamatinib), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in platelet disorders or is in consultation with a Hematologist or Transplantation Specialist (when appropriate)

2. Individual's condition has responded while on therapy with response defined as **ALL** of following:
    a. Achieved and maintains a platelet count between 50 x 10^9/L and 400 x10^9/L
    b. Has not had any platelet transfusions, fresh frozen plasma, whole blood, packed red blood cells, cryoprecipitate, vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, surgical or interventional radiology procedure to control blood loss
    c. Has not had any serious or severe bleeding events
    d. Has not had any hospitalizations for severe thrombocytopenia

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use as follows:
    a. **For Doptelet (avatrombopag):**
        i. Thrombotic or thromboembolic complications (arterial or venous)
    b. **For Alvaiz (eltrombopag) and Promacta (eltrombopag):**
        i. Thrombotic/thromboembolic complications (such as: DVT, PE, stroke, MI)
        ii. Persistent platelet count >400 x 10^9/L
        iii. Hyperbilirubinemia
        iv. Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
        v. Development or worsening of cataracts
        vi. Myelodysplastic syndrome
        vii. Acute Myeloid Leukemia
    c. **For Tavalisse (fostamatinib):**
        i. Severe hypertension despite 4 weeks of aggressive antihypertensive therapy
        ii. Hypertensive crisis (SBP > 180 and/or DBP > 120 mmHg) despite 4 weeks of aggressive therapy
        iii. Hepatotoxicity (AST/ALT persist at 5 x ULN or higher for 2 weeks or more **OR** AST/ALT is 3 x ULN or more AND total bilirubin is greater than 2 x ULN)
        iv. Persistent severe diarrhea despite use of antidiarrheal agents
        v. Persistent neutropenia (neutrophil count < 1 x 10^9/L) despite dose adjustment
        vi. Unable to use at least 100 mg daily

6. Will not be used to normalize platelet count and will not be used if the platelet count is greater than 400 x 10^9/L

7. Will not be used in combination with each other or with Mulpleta (lusutrombopag), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

8. **Additional criteria for Alvaiz or Promacta**: Will not be used to treat individuals with myelodysplastic syndromes (MDS)

9. **Additional criteria for Tavalisse only:** Individual is not using strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, others

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Section C. Chronic Liver Disease associated thrombocytopenia, pre-procedural use: DOPTELET (avatrombopag) MULPLETA (lusutrombopag)

- **Criteria for therapy:** Doptelet (avatrombopag), Mulpleta (lusutrombopag), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in platelet disorders or is in consultation with a Gastroenterologist, Hepatologist, Hematologist, or Transplantation Specialist (when appropriate)

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of ***thrombocytopenia*** in an individual with ***chronic liver disease scheduled to undergo an elective procedure***

4. The degree of thrombocytopenia and clinical condition increases the risk for bleeding **OR** has documented bleeding symptoms

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **either** of the following agents:
    a. Dexamethasone
    b. Methylprednisolone

7. Platelet count at 8-14 days before the scheduled procedure is less than 50 x 10^9/L

8. Will not be used in an attempt to normalize platelet count

9. Will not be used in combination with each other or with Alvaiz (eltrombopag), Promacta (eltrombopag), Tavalisse (fostamatinib), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

Approval duration:
For Doptelet: 5-day supply per procedure, no refills

For Mulpleta: 7-day supply per procedure, no refills

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Section D. Chronic hepatitis C thrombocytopenia from interferon-based therapy: ALVAIZ (eltrombopag) PROMACTA (eltrombopag)

- **Criteria for initial therapy:** Alvaiz (eltrombopag), Promacta (eltrombopag), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in hepatitis C or is in consultation with a Hepatologist, Gastroenterologist, or Infectious disease

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of ***chronic hepatitis C in a candidate for interferon and ribavirin*** treatment

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. The degree of thrombocytopenia limits the ability to initiate interferon **OR** individual is on interferon-based therapy, but the degree of thrombocytopenia limits the ability to continue interferon

6. Individual is not at risk for hepatic decompensation

7. Will not be used in combination with direct-acting antiviral agents without interferon and ribavirin for treatment of chronic hepatitis C infection

8. Will not be used to normalize platelet count and will not be used if the platelet count is greater than 400 x 10^9/L

9. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Platelet count is less than 75 x 10^9/L or has documented bleeding symptoms
    b. Complete blood count
    c. Liver function tests
    d. Ocular examination for detection of cataracts

10. Will not be used in combination with Doptelet (avatrombopag), Mulpleta (lusutrombopag), Tavalisse (fostamatinib), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

11. Will not be used to treat individuals with myelodysplastic syndromes (MDS)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Alvaiz (eltrombopag), Promacta (eltrombopag), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in hepatitis C or is in consultation with a Hepatologist, Gastroenterologist, or Infectious disease

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Able to initiate interferon-based therapy **or** able to continue interferon-based therapy
    b. Achieved and maintains a platelet count of above 75 x 10^9/L
    c. Has not had any platelet transfusions, fresh frozen plasma, whole blood, packed red blood cells, cryoprecipitate, vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, surgical or interventional radiology procedure to control blood loss

d. Has not had any serious or severe bleeding events
e. Has not had any hospitalizations for severe thrombocytopenia

3. Individual has been adherent with the medication and antiviral interferon and ribavirin therapy

4. Individual continues with hepatitis C antiviral regimen of interferon and ribavirin, if this regimen is stopped, Promacta (eltrombopag) will not be renewed or continued

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Will not be used to normalize platelet count and will not be used if the platelet count is greater than 400 x 10^9/L

7. Will not be used in combination with Doptelet (avatrombopag), Mulpleta (lusutrombopag), Tavalisse (fostamatinib), Nplate (romiplostim) injection, or Cablivi (caplacizumab-yhdp) injection

8. Will not be used to treat individuals with myelodysplastic syndromes (MDS)

9. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Thrombotic/thromboembolic complications (such as DVT, PE, stroke, MI)
   b. Persistent platelet count >400 x 10^9/L
   c. Hyperbilirubinemia
   d. Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
   e. Development or worsening of cataracts
   f. Myelodysplastic syndrome
   g. Acute Myeloid Leukemia

Renewal duration: 6 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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Description:

Doptelet (avatrombopag) and Mulpleta (lusutrombopag) are thrombopoietin (TPO) receptor agonist designed to mimic the effects of TPO. They are indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure that would typically require platelet transfusion. Doptelet (avatrombopag) and Mulpleta (lusutrombopag) should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. Doptelet (avatrombopag) is also indicated for chronic immune thrombocytopenia who have had an insufficient response to previous treatment.

When used as a pre-procedural agent, Doptelet (avatrombopag) dosing should begin 10-13 days prior to the scheduled procedure. The recommended daily dose of Doptelet (avatrombopag) is based on the patient's platelet count prior to the scheduled procedure. Patients should undergo their procedure 5-8 days after the last dose of Doptelet (avatrombopag). Doptelet (avatrombopag) should be taken orally once daily for 5 consecutive days all five days of dosing should be completed. Doptelet (avatrombopag) has been investigated only as a single 5-day once daily dosing regimen in clinical trials in patients with chronic liver disease. The onset of the platelet count increase was observed in clinical trials was within 3-5 days of the start of a 5-day treatment course, with peak effect observed after 10-13 days. Subsequently, platelet counts decreased gradually, returning to near baseline values after 35 days. Patients undergoing neurosurgical interventions, thoracotomy, laparotomy, or organ resection were not studied in the Doptelet (avatrombopag) clinical trials.

Mulpleta (lusutrombopag) dosing should begin 8-14 days prior to the scheduled procedure. The recommended daily dose of Mulpleta (lusutrombopag) is 3 mg once daily. A platelet count should be obtained prior to starting Mulpleta (lusutrombopag)and no more than two days before the procedure. Patients should undergo their procedure 2-8 days after the last dose of Mulpleta (lusutrombopag). Mulpleta (lusutrombopag) should be taken orally once daily for 7 consecutive days. Mulpleta (lusutrombopag) has been investigated only as a single 7-day once daily dosing regimen in clinical trials in patients with chronic liver disease. After a 3 mg dose, the median time to reach a maximum platelet count was 12 days and ranged 5-35 days. The median duration of platelet count increase was 20 days. Patients undergoing laparotomy, thoracotomy, open-heart surgery, craniotomy, or organ resection were excluded from the Mulpleta (lusutrombopag) clinical studies. Patients with a history of splenectomy, partial splenic embolization, or thrombosis and those with Child-Pugh class C liver disease, absence of hepatopetal blood flow, or a prothrombotic condition other than chronic liver disease were not allowed to participate.

Alvaiz (eltrombopag) and Promacta (eltrombopag) are oral thrombopoietin (TPO) receptor agonists indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy; for the treatment severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy; and for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy; the safety and efficacy of Alvaiz (eltrombopag) and Promacta (eltrombopag) in combination with direct-acting antiviral agents without interferon have not been established. Alvaiz (eltrombopag) and Promacta (eltrombopag) are not indicated for the treatment of patients with myelodysplastic syndrome (MDS).

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Tavalisse (fostamatinib) is a tyrosine kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Tavalisse (fostamatinib) should be discontinued after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding. Fostamatinib is a phosphate pro-drug that is converted in the gut by alkaline phosphatase into an active metabolite that is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The metabolite reduces antibody-mediated destruction of platelets.

TPO is the major physiologic endogenous regulator of platelet production. TPO is made in the liver, and it stimulates bone marrow to produce platelets. In CLD, TPO production is reduced, which consequently results in decreased platelet production and increases the likelihood for bleeding and other post-procedure complications. Thrombocytopenia is one of the most common hematologic disorders, characterized by an abnormally low number of platelets from multiple causes. Thrombocytopenia is defined as a platelet count of less than 150,000 per microliter. A normal count of thrombocytes (or platelets) is between 150,000 and 450,000 per microliter. The clinical expression of thrombocytopenia ranges from asymptomatic to life-threatening bleeding.

Patients with platelet counts greater than 50,000 per microliter rarely have symptoms. A platelet count from 30,000-50,000 per microliter may manifests as purpura. A count from 10,000-30,000 per microliter may cause bleeding with minimal trauma. A platelet count less than 5,000 per microliter may cause spontaneous bleeding and constitutes a hematologic emergency. Various syndromes and diseases are associated with thrombocytopenia.

First-line treatment for thrombocytopenia is usually use of a corticosteroid, such as prednisone or dexamethasone. Intravenous immunoglobulin (IVIG) or intravenous anti-D (Rho[D] immune globulin) can also be used as initial treatment with or without steroids. The most effective second-line treatment option is splenectomy. Other second-line treatment options that may postpone the need of splenectomy include azathioprine, cyclosporine, cyclophosphamide, danazol, vinca alkaloids, mycophenolate mofetil, rituximab, and thrombopoietin-receptor agonists or other platelet stimulating agents.

ITP is characterized by isolated thrombocytopenia often occurring in the absence of an identifiable cause. It is an autoimmune disorder with immunologic destruction of otherwise normal platelets. ITP has variably been called immune thrombocytopenic purpura, idiopathic thrombocytopenic purpura, and immune thrombocytopenia. ITP is generally considered a benign condition with severe major hemorrhage being rare, bleeding occurs primarily in those with platelet counts $< 10 \times 10^9$/L. However, bleeding episodes are highly variable; they may range from mild bruising or mucosal bleeding in a generally asymptomatic individual to frank hemorrhage from any site. For ITP, TPO receptor agonists should only be used in patients whose degree of thrombocytopenia and clinical condition increases the risk for major bleeding.

Controlled studies on the treatment of ITP are lacking. The goal of therapy, when needed, is to raise the platelet count high enough to prevent major bleeding. Patients with platelet count of $\geq 30 \times 10^9$/L generally do not require therapy. Treatment is reserved for patients who are symptomatic or if platelet count is $< 30 \times 10^9$/L. General recommendations for first line therapy consists of corticosteroids, intravenous immune globulin, or anti-D

immunoglobulin. Splenectomy offers the best chance for cure and is indicated in patients with chronic ITP and platelet counts < 30 x 10^9 per liter after first line therapy has failed.

Aplastic anemia is a rare, life-threatening disorder of bone marrow failure characterized by pancytopenia and a hypocellular bone marrow. Thrombocytopenia is a major cause of morbidity and mortality in patients with aplastic anemia. The cause of thrombocytopenia is thought to be due to decreased hematopoietic stem and progenitor cell numbers and a reduction in function, resulting in impaired synthesis of megakaryocytes and insufficient mature platelet production. Studies suggest that the ultimate mechanism leading to hematopoietic stem and progenitor depletion is an immune mediated attack and destruction.

Virtually all patients with aplastic anemia have thrombocytopenia. Individuals with platelet counts of < 50 x 10^9/L are described as having moderate aplastic anemia while platelet counts of < 20 x 10^9/L are considered as having severe aplastic anemia. Bleeding is not typically observed until the platelet count falls below 10–20 x 10^9/L. Bleeding events seen in thrombocytopenia of aplastic anemia may consist of petechiae and ecchymoses of the skin and mucous membranes, epistaxis and gingival hemorrhage.

Treatment of thrombocytopenia related to bone marrow failure consists of use of prophylactic platelet transfusions to maintain an adequate number of platelets to avoid significant bleeding, while waiting for a response to immunosuppressive treatment (IST) or allogeneic stem cell transplantation engraftment. Allogeneic bone marrow transplantation offers the best chance for cure in younger patients, but many individuals may not be suitable candidates for transplantation due to advanced age, co-morbidities, or lack of a histocompatible donor. It is estimated that individuals with SAA who are given IST, one-quarter to one-third will not respond, and 30–40% of responder's relapse. IST consists of use of the combination of Antithymocyte globulin and Cyclosporine or high dose Cyclophosphamide alone. Corticosteroids may be needed when Antithymocyte globulin is used. Tacrolimus is sometimes used as an alternative for Cyclosporine. There are no standard criteria to judge when IST has failed.

Most guidelines recommend transfusing patients with thrombocytopenia prophylactically when platelets fall to < 10 x 10^9/L, or in patients with fevers or a bleeding history with a platelet count of < 20 10^9/L. However, it is important to realize that the clinical evidence supporting transfusion thresholds remains controversial as these thresholds were primarily derived from patients with hematologic malignancies undergoing chemotherapy or stem cell transplantation, not aplastic anemia.

Thrombocytopenia from use of interferon based hepatic C therapy is well established. As the platelet count falls to below 50 x 10^9/L, interferon dose reduction is recommended. When the platelet count falls to below 30 x 10^9/L the recommendation is to discontinue interferon therapy. The mechanism of the thrombocytopenia is thought to include inhibition of proliferation of megakaryocytes, drug induced autoimmune reaction, and impaired TPO production.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

PHARMACY COVERAGE GUIDELINE

ALVAIZ™ (eltrombopag) oral
DOPTELET® (avatrombopag) oral
MULPLETA® (lusutrombopag) oral
PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
Generic Equivalent (if available)

		Treatment of Thrombocytopenia for:			
	Route	CLD Pre-procedures	Chronic ITP	Aplastic anemia	Hep C*
Alvaiz (eltrombopag)	Oral		X	X	X
Doptelet (avatrombopag)	Oral	X†	X		
Mulpleta (lusutrombopag)	Oral	X‡			
Promacta (eltrombopag)	Oral		X	X	X
Tavalisse (fostamatinib)	Oral		X		

CLD: Chronic liver disease
ITP: Immune thrombocytopenia
Hep C: Hepatitis C

* Used to allow the initiation and maintenance of interferon-based therapy in hepatitis C.

† **Doptelet** start 10-13 days before the scheduled procedure and then undergo procedure 5-8 days after the last dose. Onset of platelet increase occurs within 3-5 days of the start of treatment with a peak effect after 10-13 days. Median cumulative number of weeks with an increase > 50 x 10^9/L is 12.4 weeks (0-25).

‡ **Mulpleta** start 8-14 days before the scheduled procedure and then undergo procedure 2-8 days after the last dose. Median time to reach maximum platelet count is 12 days (5-35 days). Median duration of increase to at least 50 x 10^9/L 19-22 days (13-28)

Critical bleeding – Bleeding into a critical anatomical site or bleeding that causes hemodynamic instability or respiratory compromise. Includes intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome.

Severe bleeding – Bleeding that results in a fall in hemoglobin of 2 or more g/dL or requires transfusion of 2 or more units of pRBCs but does not meet the definition of critical bleeding.

Minor bleeding – Bleeding that does not meet criteria for severe or critical bleeding. Examples include skin bleeding or non-severe mucous membrane bleeding.

Most cases of critical and severe bleeding occur with a platelet count<20,000/microL; some a count of <30,000/microL. Some risk factors for bleeding include liver or kidney disease, anticoagulants, antiplatelet agents, and other medications that contribute to bleeding risk.

The most common glucocorticoid used for critical or severe bleeding is dexamethasone, 40 mg intravenously once per day for 4 days. Alternative glucocorticoid regimens can be used (e.g., methylprednisolone 1gram intravenously once per day for 3 days for critical bleeding, oral prednisone for minor bleeding).

PHARMACY COVERAGE GUIDELINE

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TAVALISSE™ (fostamatinib) oral
Generic Equivalent (if available)

Resources:

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