BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ALVAIZ™ (eltrombopag) oral
DOPTELET® (avatrombopag) oral
Eltrombopag oral
MULPLETA® (lusutrombopag) oral
PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
WAYRILZ™ (rilzabrutinib) 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/or 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.

Section A. Thrombocytopenia from Severe Aplastic Anemia

Medical Necessity Requirements for ALVAIZ (eltrombopag), Eltrombopag generic, and PROMACTA (eltrombopag)

PHARMACY COVERAGE GUIDELINE

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

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the patient's diagnosis or is in consultation with Hematologist or Transplantation Specialist (when appropriate)

Indication
- Severe aplastic anemia

Age Requirement
- **For generic eltrombopag, or Promacta**: 2 years of age or older as first line treatment for severe aplastic anemia
- **For Alvaiz, generic eltrombopag, or Promacta**: 18 years of age or older in refractory severe aplastic anemia

Baseline Clinical Evaluation
- The degree of thrombocytopenia and clinical condition increases the risk for bleeding **OR** has documented bleeding symptoms
- Severe aplastic anemia with at least **TWO** of:
  - Platelet count is less than 20 x 10^9/L
  - Reticulocyte count is less than 50 x 10^9/L
  - Absolute neutrophil count is less than 0.5 x 10^9/L
- Complete blood count
- Liver function tests
- Ocular exam for detection of cataracts

Alternative Therapies
- Refractory severe aplastic anemia that failed, is contraindication per FDA label, has intolerance, or is not a candidate for **ONE** of the following:
  - Antithymocyte globulin [Thymoglobulin, Atgam] with cyclosporine with or without a corticosteroid
  - Antithymocyte globulin with cyclophosphamide with or without a corticosteroid

Brand Specific Criteria
- **For Alvaiz and Promacta:** Failure, contraindication, intolerance, or is not a candidate for **generic eltrombopag**. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)
- **For Alvaiz:** Failure, contraindication, intolerance, or is not a candidate for a **generic equivalent** (If available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

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

Safety
- No concomitant use with **ANY** of the following Alvaiz, Doptelet, eltrombopag (generic and Promacta), Mulpleta, Tavalisse, Wayrilz, Nplate, or Cablivi

Additional Requirements
- **For generic eltrombopag or Promacta**: In first line treatment severe aplastic anemia, use is with standard immunosuppressive therapy
- Does not have myelodysplastic syndrome
- Will not be used to normalize platelet count

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications
- Continues to be seen by a physician specializing in platelet disorders or is in consultation with a Hematologist or Transplantation Specialist (when appropriate)

Clinical Response
- **TWO** of the following:
  - Achieved and maintains a stable platelet count **or** platelet count increased 20 x 10^9/L above baseline
  - Hemoglobin increased by greater than 1.5 g/dL **or** a reduction in RBC infusions of greater than or equal to 4 units
  - Reticulocyte count is greater than 60 x 10^9/L
  - ANC increase of 100% **or** an ANC increase greater than 0.5 x 10^9/L
  - Has not had any serious or severe bleeding events requiring rescue with **ANY** of the following:
    1. 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
  - Has not had any hospitalizations for severe thrombocytopenia

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PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
WAYRILZ™ (rilzabrutinib) oral
Generic Equivalent (if available)

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- **For Promacta:** Failure, contraindication, intolerance or is not a candidate for **generic eltrombopag**. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)
- **For Alvaiz:** Failure, contraindication, intolerance or is not a candidate for a **generic equivalent** (If available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section

Safety
- No concomitant use with **ANY** of the following Alvaiz, Doptelet, eltrombopag (generic and Promacta), Mulpleta, Tavalisse, Wayrilz, Nplate, or Cablivi
- Has not developed any significant adverse drug effects that may exclude continued use such as:
  - Thrombotic/thromboembolic complications (such as DVT, PE, stroke, MI)
  - Persistent platelet count greater than 400 x 10^9/L
  - Hyperbilirubinemia
  - Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
  - Development or worsening of cataracts
  - Myelodysplastic syndrome
  - Acute Myeloid Leukemia

Additional Requirements
- Does not have myelodysplastic syndrome
- Will not be used to normalize platelet count
- Will not be used if the platelet count is greater than 400 x 10^9/L

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe continued use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Section B. Chronic immune (idiopathic) thrombocytopenia (ITP)

PHARMACY COVERAGE GUIDELINE

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

Medical Necessity Requirements for: ALVAIZ (eltrombopag), DOPTELET (avatrombopag), Eltrombopag generic, PROMACTA (eltrombopag), TAVALISSE (fostamatinib), and WAYRILZ (rilzabrutinib)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the patient's diagnosis or is in consultation with Hematologist or Transplantation Specialist (when appropriate)

Indication

- Has a confirmed diagnosis of persistent or chronic immune (idiopathic) thrombocytopenia (ITP)

Age Requirement

- **For Alvaiz (eltrombopag):** 6 years of age or older
- **For Doptelet (avatrombopag):** 1 year of age or older
- **For Promacta (eltrombopag) and generic eltrombopag:** 1 year of age or older
- **For Tavalisse (fostamatinib):** 18 years of age or older
- **For Wayrilz (rilzabrutinib):** 18 years of age or older

Baseline Clinical Evaluation

- Has completed **ALL** the following **baseline tests** before :
  - Platelet count is less than 30 x 10^9/L or is between 30 and 50 x 10^9/L and has documented bleeding symptoms or an increased risk for bleeding
  - Liver function tests for Alvaiz, Promacta, generic eltrombopag, Tavalisse, and Wayrilz
  - Complete blood count for Alvaiz, Promacta, generic eltrombopag, and Tavalisse
  - Negative pregnancy test in a woman of childbearing potential for Tavalisse, and Wayrilz
  - Ocular examination for detection of cataracts for Alvaiz, Promacta, and generic eltrombopag
  - Blood pressure, if abnormal, antihypertensive therapy has been initiated or adjusted for Tavalisse

Alternative Therapies

- Failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
  - Corticosteroid
  - Immunoglobulin
  - Splenectomy or is not a surgical candidate

- Failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic eltrombopag Note:** Failure, contraindication or intolerance to the generic should be reported to the FDA (see Definitions section)

Brand Specific Criteria

- **For Alvaiz, Doptelet, Tavalisse, or Wayrilz**: Failure after a trial of at least three months, contraindication per FDA label, intolerance, or is not a candidate for **their generic equivalents** (if available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **For ALL** agents, they will not be used in combination or with Mulpleta, Nplate, or Cablivi
- **For Tavalisse only:** Not using strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, others
- **For Wayrilz (rilzabrutinib)** there are **NONE** of the following:
  - Use with moderate or strong CYP3A4 inducers
  - Use with moderate or strong CYP3A4 inhibitors
  - Use with proton pump inhibitors
  - Moderate to severe hepatic impairment (Child Pugh Class B C)
  - Severe renal impairment (creatinine clearance less than 46 mL/min)

Additional Requirements

- **For Alvaiz, Promacta, and generic eltrombopag**: Will not be used in the treatment of myelodysplastic syndromes (MDS)
- **For ALL** agents they will not be used:
  - To normalize platelet count
  - If the platelet count is greater than 400 x 10^9/L

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

PHARMACY COVERAGE GUIDELINE

ALVAIZ™ (eltrombopag) oral
DOPTELET® (avatrombopag) oral
Eltrombopag oral
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PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
WAYRILZ™ (rilzabrutinib) oral
Generic Equivalent (if available)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications

- Continues to be seen by a physician specializing in platelet disorders or is in consultation with a Hematologist or Transplantation Specialist (when appropriate)

Clinical Response

- Has documentation of positive clinical response to therapy defined as **ALL** of following:
  - Achieved and maintains a platelet count between 50 x 10^9/L and 400 x10^9/L
  - 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
  - Has not had any serious or severe bleeding events
  - Has not had any hospitalizations for severe thrombocytopenia

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- **For Promacta**: Failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic eltrombopag Note:** Failure, contraindication or intolerance to the generic should be reported to the FDA (see Definitions section)
- **For Alvaiz, Doptelet, Tavalisse, or Wayrilz**: Failure after a trial of at least three months, contraindication per FDA label, intolerance, or is not a candidate for **their generic equivalents** (if available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **For ALL** agents: They will not be used in combination or with Mulpleta, Nplate, or Cablivi
- **For Alvaiz (eltrombopag), Promacta (eltrombopag), and generic eltrombopag** there are **NONE** of the following:
  - Thrombotic/thromboembolic complications (such as: DVT, PE, stroke, MI)
  - Persistent platelet count greater than 400 x 10^9/L
  - Hyperbilirubinemia
  - Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
  - Development or worsening of cataracts
  - Myelodysplastic syndrome
  - Acute Myeloid Leukemia

- **For Doptelet (avatrombopag):** Has not developed thrombotic or thromboembolic complications (arterial or venous)
- **For Tavalisse** there are **NONE** of the following:
  - Use with strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, others
  - Severe hypertension despite 4 weeks of aggressive antihypertensive therapy
  - Hypertensive crisis (systolic blood pressure greater than 180 and/or diastolic blood pressure greater than 120 mmHg) despite 4 weeks of aggressive therapy
  - Hepatotoxicity (AST/ALT persists at 5 times the upper limit of normal (ULN) or higher for 2 weeks or more **OR** AST/ALT is 3 times ULN or more AND total bilirubin is greater than 2 times ULN)
  - Persistent severe diarrhea despite use of antidiarrheal agents
  - Persistent neutropenia (neutrophil count less than 1 x 10^9/L) despite dose adjustment
  - Unable to use at least 100 mg daily
- **For Wayrilz (rilzabrutinib)** there are **NONE** of the following:
  - Use with moderate or strong CYP3A4 inducers
  - Use with moderate or strong CYP3A4 inhibitors
  - Use with proton pump inhibitors
  - Moderate to severe hepatic impairment (Child Pugh Class B C)
  - Severe renal impairment (creatinine clearance less than 46 mL/min)
  - Hepatotoxicity

Additional Requirements

- **For Alvaiz, Promacta, and generic eltrombopag**: Will not be used in the treatment of myelodysplastic syndromes (MDS)
- **For ALL** agents they will not be used:
  - To normalize platelet count
  - If the platelet count is greater than 400 x 10^9/L

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe continued use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Section C. Chronic Liver Disease associated thrombocytopenia, pre-procedural use:

PHARMACY COVERAGE GUIDELINE

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

Medical Necessity Requirements for DOPTELET (avatrombopag) and MULPLETA (lusutrombopag)

Criteria for Initial Therapy:

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

Indication
- A confirmed diagnosis of thrombocytopenia in an individual with chronic liver disease scheduled to undergo an elective procedure

Age Requirement
- 18 years of age or older

Baseline Clinical Evaluation
- Platelet count is less than 50 x 10^9/L at 8–14 days before procedure
- The degree of thrombocytopenia and clinical condition increases the risk for bleeding **OR** has documented bleeding symptoms

Alternative Therapies
- Failure (trial for at least three months duration), contraindication, intolerance, or is not a candidate for:
  - Dexamethasone or methylprednisolone

Brand Specific Criteria
- Have failure, contraindication, intolerance, or is not a candidate for **their generic equivalents** (If available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- Will not be used to normalize platelet count
- No concomitant use with **ANY** of the following Alvaiz, Doptelet, eltrombopag (generic and Promacta), Mulpleta, Tavalisse, Wayrilz, Nplate, or Cablivi

Initial Therapy Criteria Approval Duration
- **Doptelet:** 5 day supply per procedure, no refills
- **Mulpleta:** 7 day supply per procedure, no refills

PHARMACY COVERAGE GUIDELINE

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

Section D. Chronic hepatitis C thrombocytopenia from interferon based therapy

Medical Necessity Requirements for ALVAIZ (eltrombopag), Eltrombopag generic, and PROMACTA (eltrombopag)

Criteria for Initial Therapy:

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

Indication
- A confirmed diagnosis of chronic hepatitis C in a candidate for interferon and ribavirin treatment but degree of thrombocytopenia limits initiation or continuation of therapy interferon and ribavirin

Age Requirement
- 18 years of age or older

Baseline Clinical Evaluation
- Platelet count less than 75 x 10^9/L or has documented bleeding symptoms
- Complete blood count, liver function tests, and ocular exam
- 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

Alternative Therapies
- Failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic eltrombopag.** [**Note:** Failure, contraindication or intolerance to the generic should be reported to the FDA]

Brand Specific Criteria
- **For Alvaiz and Promacta:** Failure, contraindication, intolerance, or is not a candidate for **generic eltrombopag**. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)
- **For Alvaiz:** Failure, contraindication, intolerance, or is not a candidate for a **generic equivalent** (If available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

PHARMACY COVERAGE GUIDELINE

ALVAIZ™ (eltrombopag) oral
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PROMACTA® (eltrombopag) oral
TAVALISSE™ (fostamatinib) oral
WAYRILZ™ (rilzabrutinib) oral
Generic Equivalent (if available)

Safety
- No concomitant use with **ANY** of the following Alvaiz, Doptelet, eltrombopag (generic and Promacta), Mulpleta, Tavalisse, Wayrilz, Nplate, or Cablivi

Additional Requirements
- No hepatic decompensation
- Will not be used to normalize platelet count
- Will not be used if the platelet count is greater than 400 x 10^9/L
- Will not be used to treat individuals with myelodysplastic syndromes (MDS)
- Will be used in combination with interferon and ribavirin

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications
- Continues to be seen by a physician specializing in hepatitis C or is in consultation with a Hepatologist, Gastroenterologist, or Infectious disease

Clinical Response
- Documentation of positive clinical response to therapy defined as the following:
  - Able to initiate interferon based therapy **or** able to continue interferon based therapy
  - Achieved and maintains a platelet count of above 75 x 10^9/L
  - 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
  - Has not had any serious or severe bleeding events
  - Has not had any hospitalizations for severe thrombocytopenia

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WAYRILZ™ (rilzabrutinib) oral
Generic Equivalent (if available)

Adherence

- Adherence to the prescribed therapy regimen, including ribavirin and interferon has been documented

Brand Specific Criteria

- **For Promacta:** Failure, contraindication, intolerance, or is not a candidate for **generic eltrombopag**. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)
- **For Alvaiz:** Failure, contraindication, intolerance, or is not a candidate for a **generic equivalent** (If available). **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with **ANY** of the following Alvaiz, Doptelet, eltrombopag (generic and Promacta), Mulpleta, Tavalisse, Wayrilz, Nplate, or Cablivi
- Has not developed any significant adverse drug effects that may exclude continued use such as:
  - Thrombotic/thromboembolic complications (such as DVT, PE, stroke, MI)
  - Persistent platelet count >400 x 10^9/L
  - Hyperbilirubinemia
  - Hepatotoxicity, liver injury or persistent elevation of LFT's or hepatic decompensation
  - Development or worsening of cataracts
  - Myelodysplastic syndrome
  - Acute Myeloid Leukemia

Additional Requirements

- No hepatic decompensation
- Will not be used to normalize platelet count
- Will not be used if the platelet count is greater than 400 x 10^9/L
- Does not have myelodysplastic syndrome
- Eltrombopag product will be discontinued if ribavirin and interferon are discontinued

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe continued use

Continuation Therapy Criteria Approval Duration

- 6 months OR end of plan year

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Generic Equivalent (if available)

Criteria for Off-Label Use Requests:

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

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).

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 x 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 ≥ 30 x 10^9/L generally do not require therapy. Treatment is reserved for patients who are symptomatic or if platelet count is < 30 x 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.

PHARMACY COVERAGE GUIDELINE

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

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

		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		
Wayrilz (rilzabrutinib)	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)

PHARMACY COVERAGE GUIDELINE

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

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).

Resources:

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