

Pharmacy Policy Bulletin

Title: Blood Modifier Agents

Policy #: Rx.01.208

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

▸ Intent:

The intent of this policy is to communicate the medical necessity criteria for **eltrombopag olamine (Promacta®)**, **fostamatinib disodium (Tavalisse™)**, **avatrombopag (Doptelet®)**, **lusutrombopag (Mulpleta®)** as provided under the member's prescription drug benefit.

▸ Description:

Idiopathic thrombocytopenia purpura (ITP): ITP is an immune disorder in which the blood doesn't clot normally. ITP can cause excessive bruising and bleeding and can be characterized as an unusually low level of platelets, or thrombocytes, in the blood results in ITP.

Thrombocytopenia in patients with hepatitis C: Thrombocytopenia can occur in patients with chronic hepatitis C virus (HCV) infection. The pathophysiology is multifactorial and includes direct bone marrow suppression, an overactive spleen, decreased production of thrombopoietin and therapeutic adverse effect all contributing to thrombocytopenia.

Aplastic Anemia: A blood disorder caused by failure of the bone marrow to make enough new blood cells. Bone marrow is a sponge-like tissue inside the bones that makes stem cells that differentiate into red blood cells, white blood cells, and platelets.

Thrombocytopenia in patients with chronic liver disease: Individuals with chronic liver disease have varying degree of thrombocytopenia which may be caused by impaired platelet production from decreased hepatic synthesis of thrombopoietin. In addition, individuals with advanced liver disease may have reduced platelet function due to coexisting uremia, infection, and/or endothelial abnormalities. These factors combined put the individuals with chronic liver disease at an increased risk for bleeding especially during procedures.

Mechanism of Action:

Eltrombopag olamine (Promacta®) tablets contain a thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO receptor which initiates

signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells ultimately increasing platelet production.

Eltrombopag olamine (Promacta®) is a thrombopoietin receptor agonist indicated for the treatment of:

- 1.) Thrombocytopenia in adult and pediatric patients 1 year and older with chronic idiopathic thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- 2.) Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. PROMACTA should only be used 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.
- 3.) Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

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

Fostamatinib disodium (Tavalisse™) tablet is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Avatrombopag (Doptelet®) and lusutrombopag (Mulpleta®) tablets contain a thrombopoietin (TPO) receptor agonist for oral administration. They stimulate proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production. Lusutrombopag induces megakaryocyte maturation by interacting with the transmembrane domain of human TPO receptor expressed on megakaryocytes.

Avatrombopag (Doptelet®) and lusutrombopag (Mulpleta®) are indicated for the treatment of thrombocytopenia associated with chronic liver disease prior to planned procedure.

Policy:

Eltrombopag olamine (Promacta®) is approved when ONE of the following is met:

1. Diagnosis of relapsed/refractory chronic immune (idiopathic) thrombocytopenic purpura (ITP) for greater than 6 months and ALL of the following:
 - a. Member is 1 year of age or older; and
 - b. Baseline platelet count is less than 50,000/mcL; and
 - c. Insufficient response to corticosteroids, immunoglobulins, or splenectomy; and
 - d. Prescribed by or in consultation with a hematologist/oncologist

OR

2. Diagnosis of severe aplastic anemia and ALL of the following
 - a. Member is 18 years of age or older; and
 - b. Inadequate response or inability to tolerate immunosuppressive therapy with antithymocyte globulin (ATG) and cyclosporine; and
 - c. Member has thrombocytopenia defined as platelet count less than 30,000/mcL; and

- d. Prescribed by or in consultation with a hematologist/oncologist

OR

3. Diagnosis of thrombocytopenia associated with hepatitis C and BOTH of the following:
 - a. Member is 18 years of age or older; and
 - b. ONE of the following:
 - i. Member has thrombocytopenia defined as platelets less than 90,000/mcL for initiation (pre-treatment) of interferon-based therapy; or
 - ii. Member has thrombocytopenia defined as platelets less than 75,000/mcL for maintenance of optimal interferon-based therapy

Approval duration:

1. Chronic immune thrombocytopenia purpura and aplastic anemia: indefinite
2. Thrombocytopenia associated with hepatitis C: 48 weeks

Fostamatinib (Tavalisse™) is approved when all of the following are met:

INITIAL CRITERIA

1. Diagnosis of chronic immune (idiopathic) thrombocytopenic purpura; AND
2. Baseline platelet count is less than 30,000/mcL; AND
3. Member's degree of thrombocytopenia and clinical condition increase the risk of bleeding; AND
4. Documentation of an inadequate response or inability to tolerate ONE of the following:
 - a. Corticosteroids
 - b. Immunoglobulins
 - c. Splenectomy
 - d. Thrombopoietin receptor agonists (e.g., Nplate®, Promacta®)
 - e. Rituximab

AND

5. Prescribed by or in consultation with a hematologist/oncologist

CONTINUATION CRITERIA

Fostamatinib (Tavalisse™) is re-approved when there is documentation of a positive clinical response to Tavalisse™ therapy as evidenced by an increase in platelet count to a level sufficient to avoid clinically important bleeding.

Authorization duration: 12 months for initial and continuation

Avatrombopag (Doptelet®) and lusutrombopag (Mulpleta®) are approved when all of the following are met:

1. Diagnosis of thrombocytopenia; AND
2. Member has chronic liver disease; AND
3. Member is scheduled to undergo a procedure; AND
4. Baseline platelet count is less than 50,000/mcL

Approval length: 1 month

Black Box Warning:

Eltrombopag olamine (Promacta®):

1. Risk for Hepatic Decompensation In Patients With Chronic Hepatitis C
 - In patients with chronic hepatitis C, eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.

2. Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

▸ Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

▸ References:

"Aplastic Anemia." Genetic and Rare Diseases Information Center, National Institute of Health, 5 July 2017, rarediseases.info.nih.gov/diseases/5836/aplastic-anemia.

Dahal, Sumit, et al. "Thrombocytopenia in Patients with Chronic Hepatitis C Virus Infection." *Advances in Pediatrics*, U.S. National Library of Medicine, 1 Mar. 2017, www.ncbi.nlm.nih.gov/pmc/articles/PMC5333732/.

Doptelet® (avatrombopag) [package insert]. Durham, NC. AkaRx, Inc. May 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210238s000lbl.pdf. Accessed January 15, 2019.

Eltrombopag olamine (Promacta®) [package insert]. Basel, Switzerland. Novartis Pharmaceuticals Co. Ltd. November 2018. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf>. Accessed January 28, 2019.


Mulpleta® (lusutrombopag) [package insert]. Florham Park, NJ. Shionogi Inc., July 2018. Available at: <https://www.shionogi.com/pdf/pi/wp-content/themes/pdfs/mulpleta.pdf>. Accessed January 28, 2019.

Shah, N. MD, Intagliata, N, MD. Hemostatic abnormalities in patients with liver disease. UpToDate. Access January 24, 2019.

"Idiopathic Thrombocytopenic Purpura (ITP)." Mayo Clinic, Mayo Foundation for Medical Education and Research, 9 Aug. 2017, www.mayoclinic.org/diseases-conditions/idiopathic-thrombocytopenic-purpura/diagnosis-treatment/drc-20352330.

Tavalisse™ (fostamatinib) [package insert]. San Francisco, CA. Rigel Pharmaceutical, Inc. April 2018. Available from: <https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf>. Accessed January 24, 2019..

▸ Applicable Drugs:

 Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Promacta®	Eltrombopag olamine
Tavalisse™	fostamatinib
Doptelet®	<u>avatrombopag</u>
Mulpleta®	<u>lusutrombopag</u>

➤ Cross References:

N/A

Policy Version Number:	3.00
P&T Approval Date:	January 10, 2019
Policy Effective Date:	April 01, 2019
Next Required Review Date:	July 12, 2019

The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.