BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 3/15/18**
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	ARCHIVE DATE:

PROMACTA® (eltrombopag olamine) oral tablet and oral suspension

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

PROMACTA® (eltrombopag olamine) oral tablet and oral suspension (cont.)

Description:

Promacta (eltrombopag) is an oral thrombopoietin (TPO) receptor agonist 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 Promacta (eltrombopag) in combination with direct-acting antiviral agents without interferon have not been established. Promacta is not indicated for the treatment of patients with myelodysplastic syndrome (MDS).

TPO is the major physiologic endogenous regulator of platelet production. It is a potent cytokine that binds to its receptor (TPO receptor or also known as cMpL) on megakaryocyte progenitor cells and it stimulates a number of signal transduction events promoting megakaryocyte proliferation, maturation, and platelet release. TPO is produced in the liver at a constant rate and cleared by TPO receptors on platelets. TPO agonists should not be used to normalize platelet counts.

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 $< 30 \times 10^9$ 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 $< 50 \times 10^9$/L are described as having moderate aplastic anemia while platelet counts of $< 20 \times 10^9$/L are considered as having severe aplastic anemia. Bleeding is not typically observed until the platelet count falls below $10–20 \times 10^9$/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.

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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 responders 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.

Promacta (eltrombopag olamine)

Medication class:

- Hematopoietic Growth Factors, Thrombopoietin Receptor

FDA-approved indication(s):

- Thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (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.
- Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Promacta 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.
- Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Limitations of use:

- Promacta is not indicated for the treatment of patients with myelodysplastic syndrome (MDS).
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

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Recommended Dose:

- **Chronic ITP:** Initiate Promacta at 50 mg once daily for most adult and pediatric patients 6 years and older and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9 /L. Do not exceed 75 mg per day.
- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate Promacta at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg.
- **Severe Aplastic Anemia:** Initiate Promacta at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9 /L. Do not exceed 150 mg per day.

Available Dosage Forms:

- Tablet: 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg

Warnings and Precautions:

- Hepatotoxicity: Monitor liver function before and during therapy.
- Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia.
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving Promacta. Monitor platelet counts regularly.

Criteria:

- **Criteria for initial therapy:** Promacta (eltrombopag olamine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Requesting provider specialty is **OR** is in consultation with **ONE** of the following:
    - Hematology
    - Hepatology
    - Gastroenterology
    - Infectious disease
    - Transplantation

2. Individual has thrombocytopenia from **ONE** of the following:
    - Chronic immune (idiopathic) thrombocytopenia in an individual 1 year of age or older severe enough to increase the risk for bleeding who has had an insufficient response to **ONE** of the following:
        - Corticosteroid
        - Immunoglobulin: **EITHER** IVIG **or** Anti-D (Rho)
        - Splenectomy **or** is not a candidate for splenectomy
    - Severe aplastic anemia in an individual 18 years of age or older, who has had an insufficient response to immunosuppressive therapy with **ONE** of the following:
        - Antithymocyte globulin with Cyclosporine with or without a Corticosteroid
        - Antithymocyte globulin [Thymoglobulin, Atgam] with or without a Corticosteroid
        - Antithymocyte globulin with Cyclophosphamide with or without a Corticosteroid

- Cyclosporine with Cyclophosphamide
- Cyclophosphamide

- Chronic hepatitis C associated thrombocytopenia that satisfies **ALL** of the following:
  - Individual is 18 years of age or older
  - Individual is a candidate for interferon-based therapy **OR** individual is on interferon-based therapy but the degree of thrombocytopenia limits the ability to initiate **or** maintain interferon
  - Hepatitis C antiviral regimen is use of interferon and ribavirin
  - Individual is not at risk for hepatic decompensation

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

4. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Comprehensive metabolic panel
   - Complete blood count
   - Ocular examination for detection of cataracts

5. Absence of **ALL** of the following exclusions:
   - Platelet count > 400 x 10^9/L
   - Liver tests abnormalities that persist, worsen, or recur from use of Promacta
   - Woman who is breast feeding an infant or child

Initial approval duration:
- Up to 50mg/day x 12 months for age 6 and older
- **OR** 25mg/day x 12 months for children 1-5 years of age

➢ **Criteria for continuation of coverage (renewal request):** Promacta (eltrombopag olamine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be in consultation with a specialist in either Hematology, Hepatology, Gastroenterology, Infectious disease, or Transplantation (when appropriate)

2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - Chronic immune (idiopathic) thrombocytopenia
       - Platelet count does not increase to a sufficient level after 4 weeks of therapy
       - Excessive platelet count responses
     - Severe aplastic anemia
       - No hematologic response after 16 weeks of therapy
       - Excessive platelet count responses
     - Chronic hepatitis C associated thrombocytopenia
       - Discontinue when antiviral therapy with interferon is discontinued
       - Excessive platelet count responses

3. The indication for use is one that requires a longer duration than the usual duration

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4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications or adverse effect:
        - Signs and symptoms may include:
            - Hyperbilirubinemia
            - ALT levels greater than 3X the upper limit of normal (ULN)
            - Clinical signs of liver injury or persistent elevation of LFT's or hepatic decompensation
            - Thrombotic/thromboembolic complications from increases in platelet counts
            - Development or worsening of cataracts

6. There are no significant interacting drugs

Renewal duration:
- Up to 50mg/day x 12 months for age 6 and older
- **OR** 25mg/day x 12 months for children 1-5 years of age 12 months

Resources:

Promacta. Package Insert. Revised by manufacturer 10/2017. Accessed 2/23/18.

Promacta (eltrombopag) package insert. Revised by manufacturer 03-2017. Accessed 06-29-2017.

Promacta (eltrombopag). Package Insert. Revised by manufacturer 09-2015. Accessed 05-23-2016.

Promacta (eltrombopag). Package Insert. Revised by manufacturer 08-2014. Accessed 04-21-2015.

Marsh J.: Current aplastic anemia guidelines and unresolved problems. Cellular Therapy and Transplant 2010; 3 (9): 1-4.

DeZern AE, Brodsky RA.: Clinical management of aplastic anemia. Expert Rev Hematol 2011 April; 4(2): 221-230 NIH Public Access.

Lin KH, Hsu PI, Yu HC, et al.: Factors related to severe thrombocytopenia during antiviral therapy in patients with chronic hepatitis c and pretreatment low platelet counts. BMC Gastroenterol 2012, 12:7.

Kuter DL: The biology of thrombopoietin and thrombopoietin receptor agonists. In J Hematol 2013 98: 10-23.

Townsley DM, Desmond R, Dunbar CE, Young NS: Pathophysiology and management of thrombocytopenia in bone marrow failure: possible clinical applications of TPO receptor agonists in aplastic anemia and myelodysplastic syndromes. In J Hematol 2013 98: 48-55.

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.