

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru180

Topic: Promacta[®], eltrombopag

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Eltrombopag (Promacta[®]), available in oral tablet, is a protein that increases platelet production. Due to serious safety concerns, members who use eltrombopag need to be enrolled in a manufacturer-sponsored safety monitoring program.

Policy/Criteria

- I.** Most contracts require prior authorization of eltrombopag prior to coverage. Eltrombopag may be considered medically necessary in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) when all of the following criteria A, B, and C below are met.

A. A diagnosis of chronic ITP made by, or in consultation with, a hematologist.

AND

B. Patient is at risk of spontaneous bleeding as demonstrated in chart notes by either one of the following criteria 1 or 2 below:

1. Platelet count less than 20,000/mm³.

OR

2. Platelet count less than 30,000/mm³ accompanied by symptoms of bleeding.

AND

C. Treatment with at least one the following ITP treatments was ineffective or not tolerated:

1. Adequate course of systemic corticosteroids (e.g., prednisone 1 to 2 mg/kg for 2 to 4 weeks, or pulse dexamethasone 40 mg daily for 4 days).

OR

2. Immunoglobulin replacement.

OR

3. Splenectomy.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence considers eltrombopag to be a self-administered medication.

B. When prior authorization is approved, eltrombopag may be initially authorized for a period of 6 weeks.

- C. When prior authorization is approved, eltrombopag may be authorized in quantities of up to one tablet per day, not exceeding 75 mg per day.
- D. Authorization shall be reviewed at least every six months to confirm that the patient's recent (within the last 90 days) platelet count is either:
 - 1. Equal to or greater than 30,000/mm³ but not more than 150,000/mm³.

OR

- 2. Less than 30,000/mm³ but platelet counts have increased from baseline accompanied with a resolution of previous bleeding.

III. Eltrombopag is considered not medically necessary when used for all other conditions, including, but not limited to:

- A. Acute thrombocytopenia.
- B. Low platelet counts secondary to other conditions or diseases (including, but not limited to, cancer, HIV, hepatitis, and myelodysplastic syndrome).
- C. Drug-induced thrombocytopenia (e.g., chemotherapy, heparin).
- D. Thrombocytopenia secondary to disseminated intravascular coagulation, hemangiomas, or platelet loss (massive bleeding).
- E. Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS).

Position Statement

Summary

- Eltrombopag is a protein used to increase platelet production in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.^[1]

- Standard treatments for chronic ITP include corticosteroids, immunoglobulins, and splenectomy. Therapy for refractory ITP includes: danazol, rituximab, immunosuppressant agents (e.g., cyclosporine, azathioprine), chemotherapeutic agents (e.g., cyclophosphamide, vincristine), dapsone, IV/PO corticosteroids, anti-rho D, and interferon, among others^[5].
- There is insufficient reliable evidence to determine the value of eltrombopag for patients with chronic ITP. Due to risk of rare but serious side effects and uncertain long term benefit, eltrombopag should only be reserved for very refractory patients when other treatments options have been ineffective.
- It is uncertain whether the increase in platelets with eltrombopag is sustainable and whether eltrombopag decreases bleeding episodes or other complications in patients with chronic ITP.
- A normal platelet count in a healthy person is between 150,000 and 400,000/mm³. The goal of treatment for chronic ITP should be to maintain a safe platelet count to decrease risks for bleeding, not to achieve a normal platelet count.^[8]
- Risk of spontaneous bleeding increases as platelet counts drops below 20,000 per mm³.^[9]
- Eltrombopag is available only through a restricted distribution program called PROMACTA CARES Program. Under this Program, only prescribers and patients registered with the program are able to prescribe, administer, and receive eltrombopag^[1].
- Around one-third of patients may expect a long-term response from treatment with an oral corticosteroid. Corticosteroids should be rapidly tapered and stopped in patients who fail to respond after 4 weeks.^[6]
- Up to two-thirds of patients with ITP who undergo splenectomy may achieve a normal platelet count, which is often sustained with no additional therapy.^[5,6]
- Romiplostim (NplateTM), a platelet growth factor with similar mechanism of action to eltrombopag, may maintain platelet counts above 50,000/mm³ in one-third to one-half of chronic ITP patient. However, its long-term value past 24 weeks is also unknown^[10].
- Eltrombopag and romiplostim are both linked to similar serious side effects that need to be carefully weighed against their short-term potential benefit^[1,11].

Clinical Efficacy

- Two randomized-controlled studies of up to 6 months in duration compare eltrombopag to placebo in 311 patients with chronic ITP^[1,3,4]. The evidence suggests that:
 - * Eltrombopag may increase platelet counts; however, its effectiveness past 6 months is uncertain.
 - * Because the risk of bleeding is only prominent when platelet count drops below 20,000/mm³, it is difficult to quantify the clinical benefit of treatment when half of the patients in the studies had platelet count above 20,000/mm³ at baseline.
- Unreliable evidence from one 80-week open-label study in 207 patients with chronic ITP suggests that the effectiveness of eltrombopag may decrease significantly over time. At week 52, only 2 out of 207 patients were able to maintain platelet count >50,000/mm³ continuously^[1].
- There are no studies evaluating the efficacy of eltrombopag compared to other standard treatments.

Safety

- Uncommon but serious side effects include:
 - * **Bone marrow changes:** eltrombopag increases the risk for reticulin deposition within the bone marrow. Clinical studies have not ruled out the possibility that reticulin and other fiber deposition may result in bone marrow fibrosis with cytopenias.
 - * **Worsening low blood platelet count:** discontinuation of eltrombopag may result in worsened thrombocytopenia than was present prior to eltrombopag therapy and increased risk for bleeding.
 - * **High platelet counts and increased risk of blood clots:** eltrombopag may increase platelet counts to a level that produces thrombotic/thromboembolic complications.
 - * **Worsening hematologic conditions:** romiplostim may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome.

- More common adverse reactions are nausea, vomiting, menorrhagia, myalgia, paresthesia, cataract, dyspepsia, ecchymosis, thrombocytopenia, increased ALT/AST and conjunctival hemorrhage. ^[1]

References

1. Product Dossier: Promacta[®] (eltrombopag). GlaxoSmithKline: Research Triangle Park, NC; January 2009.
2. Promacta[®] (eltrombopag) Product Information. GlaxoSmithKline, Research Triangle Park, NC, November 2008.
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4. FDA Center for Drug Evaluation and Treatment. Approval package for application number NDA 022291 (eltrombopag); Medical Review. Available at: http://www.fda.gov/cder/foi/nda/2008/022291s000_TOC.htm. Accessed February 25, 2009.
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6. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Guideline. *British Journal of Hematology*, 2003, 120, 574–596.
7. Psaila B, Bussel JB. Immune thrombocytopenic purpura. *Hematol Oncol Clin North Am* – 01-AUG-2007; 21(4): 743-59, vii.
8. Kojouri K, George JN. Recent advances in the treatment of chronic refractory immune thrombocytopenic purpura. *Int J Hematol*. 2005;81(2):119-25.

9. Marini J, Wheeler A. Transfusion and blood component therapy. In: Wolters Kluwer Health, editors. Critical Care Medicine. Lippincott Williams & Wilkins, 2005. p. 251.
10. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomized controlled trial. Lancet. 2008 Feb 2;371(9610):395-403.
11. Nplate™ (Romiplostim) Product Information. Amgen Inc. Thousand Oaks, CA, March 2008.
12. Nplate™ (Romiplostim) Medication guide. Amgen Inc. Thousand Oaks, CA, August 2008.

Appendix A: American Society of Hematology – Criteria for the Diagnosis of Chronic Immune Thrombocytopenic Purpura : Diagnosis of Exclusion

- History compatible with the diagnosis of chronic ITP
- Normal physical examination findings except for signs of thrombocytopenia (petechiae, purpura, or mucosal bleeding); no adenopathy or splenomegaly
- Complete blood count showing isolated thrombocytopenia with large platelets but no anemia unless bleeding or immune hemolysis is present
- Bone marrow examination showing normal or increased numbers of megakaryocytes (not required for diagnosis unless unusual manifestation or age >60 yr.)
- No clinical or laboratory evidence for other causes of thrombocytopenia

Cross References		
Immune Globulin Replacement Therapy (IVIG, SQ) dru020		
Romiplostim (Nplate™) dru162		

Codes	Number	Description