



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Eltrombopag (Promacta®)**

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not 2010 CIGNA

Coverage Policy

CIGNA covers eltrombopag (Promacta®) for the treatment of thrombocytopenia in individuals with chronic immune (idiopathic) thrombocytopenic purpura (ITP) when BOTH of the following criteria are met:

- insufficient response to corticosteroids, immunoglobulins, or splenectomy
- degree of thrombocytopenia and clinical condition increase the risk for bleeding

FDA Approved Indications

Promacta is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic 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 increases the risk for bleeding. Promacta should not be used in an attempt to normalize platelet counts.

FDA Recommended Dosing

Initiate Promacta at a dose of 50 mg once daily. For patients with moderate or severe hepatic impairment, initiate Promacta at a reduced dose of 25 mg once daily.

Promacta is only available through a restricted distribution program called Promacta Cares which consists of a patient registry and a requirement for prescribers to complete and report baseline and periodic safety information for every patient. Prescribers, pharmacists, and patients must be enrolled in Promacta Cares in

order to prescribe, dispense and receive Promacta. Goal of enrollment is to ensure that all patients treated with Promacta are monitored appropriately and evaluated every 6 months to determine if continued treatment with Promacta is appropriate.

Drug Availability

The 25 mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side and are available in bottles of 30. The 50 mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side and are available in bottles of 30.

General Background

Disease Overview

There are two types of ITP - acute (temporary or short-term) and chronic (long-lasting). Acute ITP generally lasts less than 6 months. It mainly occurs in children, both boys and girls, and is the most common type of ITP. It often occurs after a viral infection. Chronic ITP is long-lasting (6 months or longer) and mostly affects adults. However, some teenagers and even younger children can get this type of ITP. Chronic ITP affects women 2 to 3 times more often than men. Treatment depends on how severe the bleeding symptoms are and the platelet count. In mild cases, treatment may not be needed.

Pharmacology

Eltrombopag is a small molecule TPO receptor agonist that stimulates platelet production. Eltrombopag is 52% absorbed with peak plasma concentrations occurring within 2 to 6 hours. Platelet counts begin to increase at 5 to 8 days and peak at 15 to 16 days after starting therapy. The half-life of eltrombopag is 26 to 35 hours in patients with ITP. Eltrombopag is extensively metabolized in the liver through oxidation by CYP1A2 and CYP2C8 and primarily excreted in the feces.

Clinical Efficacy

Three experimental trials and two open-label non-randomized studies evaluate eltrombopag in ITP. In 118 patients with chronic ITP, eltrombopag 50 mg or 75 mg daily for 6 weeks raised platelet counts to $\geq 50,000/\mu\text{L}$ on day 43 in 70% to 81% of patients compared to placebo at 11% ($p < 0.001$). No difference in response rate was detected between splenectomized and non-splenectomized patients. An open-label extension trial is ongoing to determine long term efficacy and safety.

There are no comparative studies between eltrombopag and romiplostim. The primary endpoints used in the efficacy trials for romiplostim and eltrombopag are different. In the romiplostim trials, the primary endpoint was durable platelet response, defined as a platelet count $\geq 50,000/\mu\text{L}$ for any 6 of the last 8 weeks of treatment. For eltrombopag, the primary endpoint was platelet counts $\geq 50,000/\mu\text{L}$ on day 43. Another difference noted between the two TPO agonists is that the overall response to romiplostim was lower in splenectomized patients than non-splenectomized patients; however, both groups were superior to placebo. In the eltrombopag clinical trial, no difference in response was detected between splenectomized and non-splenectomized patients.

Ongoing Studies

Ongoing investigational indications for Promacta include thrombocytopenia associated with chronic hepatitis C virus and chronic liver disease and oncology-related thrombocytopenia. There is one published clinical trial evaluating eltrombopag for use in patients with thrombocytopenia and cirrhosis secondary hepatitis C.

One study randomized 74 patients who had cirrhosis secondary to chronic hepatitis C infection and platelet counts between $20,000/\mu\text{L}$ and $70,000/\mu\text{L}$ to receive either eltrombopag 30, 50, or 75 mg or placebo for 4 weeks. Patients who had platelet counts $> 70,000/\mu\text{L}$ after 4 weeks of therapy were eligible to receive eltrombopag or placebo in combination with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin for 12 weeks. More than 75% of patients in each eltrombopag group had platelet counts $> 100,000/\mu\text{L}$ after 4 weeks of therapy compared to no patients in the placebo group ($p < 0.001$). Antiviral therapy with peginterferon and ribavirin was started in 49/74 patients. More patients completed 12 weeks of antiviral therapy in the eltrombopag 75 mg group, eltrombopag 50 mg group, and eltrombopag 30 mg group compared to placebo. Overall, eltrombopag increased platelet counts sufficiently in patients with cirrhosis secondary to hepatitis C to allow initiation of antiviral treatment. Additional studies are ongoing to evaluate the efficacy and safety of eltrombopag in patients with hepatitis C.

Adverse Reactions / Drug Interactions

The most common adverse effects with eltrombopag include nausea, vomiting, menorrhagia, myalgia, paresthesia, dyspepsia, and ecchymosis. In clinical trials, headache was also reported. The most common serious adverse effects include hemorrhage, liver function test abnormalities and thrombotic or thromboembolic complications. Eltrombopag carries a black box warning for hepatotoxicity and liver function test monitoring is required.

Eltrombopag has many potential drug-drug interactions. Eltrombopag is a substrate of CYP1A2 and CYP2C8, and its levels are affected by known inhibitors and inducers of these enzymes. Eltrombopag is also an inhibitor of organic anion transporting polypeptide (OATP1B1). Medications like the HMG-CoA reductase inhibitors, methotrexate, rifampin, or nateglinide, which are OATP1B1 substrates, may require a dose reduction. Eltrombopag is also an inhibitor of UDP-Glucuronosyl-transferases (UGT), which may cause increased levels of acetaminophen, narcotics and nonsteroidal anti-inflammatory medications.

Coding/Billing Information

Note: This section is not in use.

References

1. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol.* Jun 2008;48(6):1000-1007.
2. Bussel JB, B. P, Saleh MN, et al. Efficacy and Safety of Repeated Intermittent Treatment with Eltrombopag in Patients with Chronic Idiopathic Thrombocytopenic Purpura. 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
3. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med.* Nov 29 2007;357(22):2237-2247.
4. Bussel JB, Cheng G, Saleh MN, et al. Safety and Efficacy of Long-Term treatment with Oral Eltrombopag for Chronic Idiopathic Thrombocytopenic Purpura. 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
5. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med.* Oct 19 2006;355(16):1672-1681.
6. Bussel JB, Provan A, Shamsi T, et al. Eltrombopag Raises Platelet Count and Reduces Bleeding Compared with Placebo During Short-term Treatment in Chronic Idiopathic Thrombocytopenic Purpura: A Phase III Study. Paper presented at: 12th Congress of the European Hematology Association, 2007; Weill Medical College Cornell University, New York.
7. Cheng G, Bussel JB, Saleh MN, et al. Eltrombopag Delivers Clinical Benefit in Chronic Idiopathic Thrombocytopenic Purpura (ITP) Patients Not Achieving Platelet Counts $\geq 50,000/\mu\text{L}$ - Data from the EXTEND Study. 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
8. Cheng G, Saleh MN, Bussel JB, et al. Oral Eltrombopag for the Long-Term Treatment of Patients with Chronic Idiopathic Thrombocytopenic Purpura: Results of a Phase III, Double-Blind, Placebo-Controlled Study (RAISE). 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
9. Chong BH, Ho SJ. Autoimmune thrombocytopenia. *Journal of Thrombosis and Haemostasis.* 2005;3:1763-1772.

10. Erickson-Miller CL, Delorme E, Tian S, Hopson CB, J. LA, Valoret EI. Preclinical Activity of Eltrombopag (SB-497115), an Oral, Non-peptide Thrombopoietin Receptor Agonist. *Stem Cells*. Nov 2008;1-18.
11. Finnish Medical Society Duodecim. Thrombocytopenia. In *EBM Guidelines. Evidence-Based Medicine [Internet]*. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007.
12. Fogarty PF, Bussel JB, Cheng G, et al. Oral Eltrombopag Treatment Reduces the Need for Concomitant Medications in Patients with Chronic Idiopathic Thrombocytopenic Purpura. 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
13. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. *Current Opinion in Hematology*. 2007;14():515-519.
14. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996;88:3-40.
15. Giannini EG, Savarino V. Thrombocytopenia in liver disease. *Curr Opin Hematol*. Sep 2008;15(5):473-480.
16. GlaxoSmithKline. Promacta® (eltrombopag) prescribing information. Research Triangle Park, NC: GlaxoSmithKline. November 2008.
17. Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. *Blood*. Jun 1 2007;109(11):4739-4741.
18. Kumagai Y, Fujita T, Ozaki M, et al. Pharmacodynamics and pharmacokinetics of AMG 531, a thrombopoiesis-stimulating peptibody, in healthy Japanese subjects: a randomized, placebo-controlled study. *J Clin Pharmacol*. Dec 2007;47(12):1489-1497.
19. Kuter DJ. New drugs for familiar therapeutic targets: thrombopoietin receptor agonists and immune thrombocytopenic purpura. *Eur J Haematol Suppl*. Feb 2008(69):9-18.
20. Kuter DJ. Thrombopoietin and Thrombopoietin Mimetics in the Treatment of Thrombocytopenia. *Annu. Rev. Med*. 2009;60:33.31-33.14.
21. Levy B, Arnason JE, Bussel JB. The use of second-generation thrombopoietic agents for chemotherapy-induced thrombocytopenia. *Current Opinion in Oncology*. 2008;20:690-696.
22. McEvoy GK, ed. *AHFS 2010 Drug Information*. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2010.
23. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med*. Nov 29 2007;357(22):2227-2236.
24. National Heart, Lung, and Blood Institute. Diseases and Conditions Index. What Is Idiopathic Thrombocytopenic Purpura? August 2007. Retrieved 12/29/08 at http://www.nhlbi.nih.gov/health/dci/Diseases/ltp/ITP_WhatIs.html
25. Newland A. Emerging strategies to treat chronic immune thrombocytopenic purpura. *Eur J Haematol Suppl*. Feb 2008(69):27-33.
26. News Medical Net. FDA approves GSK's Promacta (Eltrombopag) Available at: <http://www.news-medical.net/?id=43244>.
27. Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. *British Journal of Haematology*. 2008;143:16-26.

28. Saleh MN, Bussel JB, Cheng G, Meddeb B, Burgess PM. Eltrombopag Is Efficacious in Patients with Refractory Chronic Idiopathic Thrombocytopenic Purpura (ITP) - Data from the EXTEND study. 50th ASH Annual Meeting and Exposition, Dec. 6-9. San Francisco, CA; 2008.
29. Schwartz RS. Immune thrombocytopenic purpura--from agony to agonist. *N Engl J Med.* Nov 29 2007;357(22):2299-2301.
30. Stasi R, Evangelista ML, Amadori S. Novel thrombopoietic agents: a review of their use in idiopathic thrombocytopenic purpura. *Drugs.* 2008;68(7):901-912.
31. Stasi R, Evangelista ML, Stipa E, Buccisano F, Venditti A, Amadori S. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemost.* Jan 2008;99(1):4-13.
32. Tillmann HL, Patel K, McHutchison JG. Role of growth factors and thrombopoietic agents in the treatment of chronic hepatitis C. *Curr Gastroenterol Rep.* Feb 2009;11(1):5-14.
33. Tiu RV, Sekeres MA. The role of AMG-531 in the treatment of thrombocytopenia in idiopathic thrombocytopenic purpura and myelodysplastic syndromes. *Expert Opin Biol Ther.* Jul 2008;8(7):1021-1030.
34. Wei A, Jackson SP. Boosting platelet production. *Nat Med.* Sep 2008;14(9):917-918.

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