# eltrombopag (Promacta®)

**Policy #** 00627
Original Effective Date: 01/01/2019
Current Effective Date: 01/01/2019

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

**When Services May Be Eligible for Coverage**
*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider eltrombopag (Promacta®)‡ for the treatment of thrombocytopenia to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for eltrombopag (Promacta) will be considered when the following criteria are met:

- Patient has a diagnosis of chronic immune thrombocytopenia (ITP) and meets ONE of the following:
  - Has tried and failed (e.g. intolerance or inadequate response) corticosteroids; OR
  - Has tried and failed (e.g. intolerance or inadequate response) immunoglobulin therapy (e.g. intravenous immunoglobulin [IVIG]); OR
  - Has had a splenectomy; OR
- Patient has chronic hepatitis C and thrombocytopenia; AND
  - Promacta will be used to initiate or maintain interferon therapy; OR
- Patient has a diagnosis of severe aplastic anemia.

**When Services Are Considered Investigational**
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of eltrombopag (Promacta) when patient selection criteria are not met to be **investigational.***

## Background/Overview

Promacta belongs to the class of drugs known as thrombopoietin receptor agonists and has three indications. Promacta is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year of age and older with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. It is also indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy and for the treatment of patients with severe aplastic anemia. It is available as a tablet in various strengths (12.5 mg, 25 mg, 50 mg, 75 mg) and as an oral suspension powder for reconstitution (25 mg packets). The recommended dose depends on the indication, the patient's age and race, and the patient's response to the initial dose, but all doses should be given on an empty stomach and be separated from other medications, calcium-rich foods,

or supplements by at least 2 hours. Promacta has a Boxed Warning regarding the risk for hepatic decompensation in patients with chronic hepatitis C infection. The safety and efficacy of Promacta have not been established in combination with direct-acting antiviral agents indicated for the treatment of chronic hepatitis C genotype 1 infection.

**Chronic Immune Thrombocytopenia (ITP)**
Chronic ITP is an acquired condition of thrombocytopenia in which autoantibodies destroy the platelets and also affect megakaryocytes and impair platelet production. ITP has previously been called idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura, or autoimmune thrombocytopenic purpura, but these terms have been replaced by immune thrombocytopenia (ITP) to reflect the known immunologic mechanism and absence of purpura in some patients. The 2011 American Society of Hematology (ASH) guidelines state that first-line treatment for adults with ITP includes corticosteroids or IVIG. For patients who are unresponsive or relapse after initial therapy, splenectomy is recommended. Thrombopoietin receptor agonists are recommended for patients with a bleeding risk who relapse following splenectomy, or have a contraindication to splenectomy and who have failed at least one other therapy. The guidelines also suggest that thrombopoietin receptor agonists be considered for those at risk of bleeding who have failed one line of therapy, such as corticosteroids or IVIG, and who have not undergone splenectomy. While there is less evidence in children, thrombopoietin receptor agonists are recommended as a second-line therapy after corticosteroids or IVIG in pediatric patients. Rituximab is another second-line treatment option for patients who have failed corticosteroids or IVIG.

**Chronic Hepatitis C**
Promacta is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should only be used in patients with hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. Patients in the trials were adults with chronic hepatitis C who were receiving either PegIntron or Pegasys, along with ribavirin, and platelet counts were $<75 \times 10^9$/L. Use of Promacta allowed approximately 95% of patients to initiate therapy and a statistically significantly greater proportion of patients given Promacta achieved sustained virologic response (SVR).

**Aplastic Anemia**
Aplastic anemia is a disorder of the hematopoietic stem cells that causes pancytopenia and a hypocellular bone marrow without splenomegaly, most often due to immune injury to multipotent hematopoietic stem cells. If untreated, aplastic anemia is associated with very high mortality. Despite these patients already having elevated levels of thrombopoietin, there is some evidence that Promacta may be effective in improving hematologic parameters in aplastic anemia. Immunosuppressive therapy (e.g., horse antithymocyte globulin, cyclosporine A) and hematopoietic cell transplantation are often used as first line treatment options before Promacta. The addition of Promacta to immunosuppressive therapy has been shown to improve cytopenias.

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## FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Promacta is approved for the treatment of thrombocytopenia in adult and pediatric patients 1 year of age and older with chronic ITP who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy. It is also indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy and for the treatment of patients with severe aplastic anemia.

## Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**Chronic ITP**

The efficacy and safety of Promacta in adult patients with chronic ITP were evaluated in 3 randomized, double-blind, placebo-controlled trials and in an open-label extension trial.

In trials 1 and 2, patients who had completed at least one prior ITP therapy and who had a platelet count less than 30 x $10^9$/L were randomized to receive either Promacta or placebo daily for up to 6 weeks followed by 6 weeks off therapy. Trial 1 randomized 114 patients (2:1) to Promacta 50 mg or placebo. Trial 2 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of Promacta, 30 mg, 50 mg, or 75 mg each administered daily. The efficacy was evaluated by response rate, defined as a shift from a baseline platelet count of less than 30 x $10^9$/L to greater than or equal to 50 x $10^9$/L at any time during the treatment period. In both trials, the response rate of Promacta 50 mg daily was statistically significantly higher than placebo (Trial 1: 59% vs 16%. Trial 2: 70% vs 11%).

In trial 3, 197 patients were randomized (2:1) to receive either Promacta 50 mg once daily or placebo for 6 months during which time the dose of Promacta could be adjusted based on individual platelet counts. Approximately half of the patients included in the trial were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts less than or equal to 15 x $10^9$/L. The efficacy of Promacta was evaluated by the odds of achieving a platelet count greater than or equal to 50 x $10^9$/L and less than or equal to 400 x $10^9$/L for patients receiving Promacta relative to placebo and was based on patient response profiles throughout the 6-month treatment period. In 134 patients who completed 26 weeks of treatment, a sustained platelet response was achieved by 60% of patients treated with Promacta compared with 10% of patients treated with placebo. Patients treated with Promacta were significantly more likely to achieve a platelet count between 50 x $10^9$/L and 400 x $10^9$/L during the entire 6 month period compared with those patients treated with placebo.

The efficacy and safety of Promacta in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials (trials 4 and 5). The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose was reduced if the platelet count exceeded 200 x $10^9$/L and interrupted and reduced if it exceeded 400 x $10^9$/L. In trial 4, patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x $10^9$/L were stratified by age and randomized (2:1) to Promacta or placebo. The efficacy of Promacta in this trial was evaluated by the proportion of subjects on Promacta achieving platelet counts $\geq$50 x $10^9$/L for at least 6 out of 8 weeks between Weeks 5 to 12. 41% of the patients in the Promacta group met this primary endpoint compared to 3% of placebo patients. More pediatric patients treated with Promacta (75%) compared with placebo (21%) had at least one platelet count $\geq$50 x $10^9$/L during the first 12 weeks of randomized treatment in absence of rescue therapy. In trial 5, 67 patients refractory or relapsed to at least one prior ITP therapy with a platelet count < 30 x $10^9$/L were stratified by age and randomized (2:1) to Promacta or placebo. The efficacy of Promacta in this trial was evaluated by the proportion of patients achieving platelet counts $\geq$50 x $10^9$/L at least once between Weeks 1 and 6 of the randomized, double-blind period. Overall, 62% of the patients in the Promacta group achieved this endpoint compared to 32% of those in the placebo group.

**Chronic Hepatitis C-associated Thrombocytopenia**
The efficacy and safety of Promacta for the treatment of thrombocytopenia in adult patients with chronic hepatitis C were evaluated in two randomized, double-blind, placebo-controlled trials. Trial 1 utilized peginterferon alfa-2a (Pegasys®)‡ plus ribavirin for antiviral treatment and Trial 2 utilized peginterferon alfa-2b (Pegintron®)‡ plus ribavirin. In both trials, patients with a platelet count of less than 75 x $10^9$/L were enrolled and stratified by platelet count, screening hepatitis C virus ribonucleic acid (HCV RNA), and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease with Child-Pugh score greater than 6 (class B and C), history of ascites, or hepatic encephalopathy. The trials consisted of 2 phases—a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label Promacta to increase the platelet count to a threshold of $\geq$90 x $10^9$/L for Trial 1 and $\geq$100 x $10^9$/L for Trial 2. Promacta was administered an initial dose of 25 mg once daily for 2 weeks and increased in 25-mg increments over 2 to 3 week periods for up to 9 weeks to achieve the optimal platelet count. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of Promacta at the end of the pre-treatment phase or to placebo. Promacta was administered in combination with pegylated interferon and ribavirin per their respective prescribing information for up to 48 weeks. The efficacy of Promacta for both trials was evaluated by SVR defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. In trial 1 (n=715), 23% of patients achieved SVR in the Promacta group compared to 14% in the placebo group. In trial 2, 19% of patients achieved SVR in the Promacta group versus 13% in the placebo group. Both of these results were statistically significant.

**Severe Aplastic Anemia**
Promacta was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count $\leq$30 x $10^9$/L. Promacta was administered at an initial dose of 50 mg once daily for 2 weeks

and increased over 2-week periods up to a maximum dose of 150 mg once daily. The efficacy was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to 20 x $10^9$/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a reduction in $\geq$ 4 units of red blood cell transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% or an ANC increase greater than 0.5 x $10^9$/L. 17 of the 43 patients (40%) achieved a hematologic response and the median duration of response was not reached.

## References

1. Promacta [package insert]. Novartis. East Hanover, NJ. May 2018.
2. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.*2011;117:4190-4207.
3. Express Scripts Promacta prior authorization policy. Updated June 2017.

## Policy History

Original Effective Date: 01/01/2019
Current Effective Date: 01/01/2019
10/04/2018 Medical Policy Committee review
10/17/2018 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2019

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.