Thrombopoietin Receptor Agonists Prior Authorization with Quantity Limit Program Summary

For BCBSAL, Nplate is not targeted in this program. Nplate is listed for information purpose only.
This criteria applies to Commercial, NetResults A series, NetResults F series and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the prior authorization (PA) requirement for Promacta and Tavalisse is to encourage appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling.

TARGET DRUGS
Promacta® (eltrombopag)
Tavalisse™ (fostamatinib disodium hyxahydrate)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Promacta® (eltrombopag) oral tablet			
12.5 mg tablet	82405030100310	M, N, O, or Y	1 tablet/day
25 mg tablet	82405030100320	M, N, O, or Y	1 tablet/day
50 mg tablet	82405030100330	M, N, O, or Y	2 tablets/day
75 mg tablet	82405030100340	M, N, O, or Y	2 tablets/day
Tavalisse™ (fostamatinib disodium hexahydrate)			
100 mg tablet	85756040100310	M, N, O, or Y	2 tablets/day
150 mg tablet	85756040100320	M, N, O, or Y	2 tablets/day

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Promacta® or Tavalisse™ will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
2. ONE of the following:
   a. The request is for Promacta and the diagnosis is hepatitis C associated thrombocytopenia and ONE of the following:
      i. The patient's platelet count is <75 x10^9/L AND the intent is to increase platelet counts sufficiently to initiate interferon therapy
      OR
      ii. The patient is on concurrent therapy with a pegylated interferon and ribavirin AND is at risk for discontinuing HCV therapy due to thrombocytopenia

   OR

   b. The request is for Promacta and the diagnosis is severe aplastic anemia and ALL of the following:

i. ALL of the following:
   A. At least 2 of the following blood criteria:
      1. Neutrophils less than 0.5 X 10^9/L
      2. Platelets less than 20 X 10^9/L
      3. Reticulocytes less than 1% corrected (percentage of actual hematocrit [Hct] to normal Hct) or reticulocyte count <20 X 10^9/L

      AND
   B. At least 1 of the following marrow criteria:
      1. Severe hypocellularity: <25%

         OR
      2. Moderate hypocellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells

AND

ii. ONE of the following:
   A. The patient has had an insufficient response to immunosuppressive therapy (defined as failure to antithymocyte globulin (ATG) and cyclosporine)

      OR
   B. The patient has an FDA labeled contraindication, intolerance, or hypersensitivity to ATG and cyclosporine

OR

c. The request is for either Promacta and the patient has the diagnosis of chronic idiopathic thrombocytopenia (ITP) with a platelet count ≤30 x 10^9/L OR 30 x 10^9/L to < 50 x 10^9/L with symptomatic bleeding or with increased risk for bleeding) and ONE of the following:
   i. The patient has had an insufficient response to a splenectomy or single treatment with corticosteroids or immunoglobulins (IVIg or anti-D)

      OR
   ii. The patient is NOT a candidate for single treatment with ALL of the following: splenectomy, corticosteroids, and immunoglobulins (IVIg or Anti-D) [i.e. documented intolerance, FDA labeled contraindication or hypersensitivity to corticosteroids/immunoglobulins]

OR

d. The patient has another FDA approved indication for the requested agent

AND

3. ONE of the following:
   a. The quantity (dose) requested is less than or equal to the program quantity limit

      OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

         AND
      ii. The requested quantity (dose) is less than or equal to the FDA labeled dose

         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit.

   OR
   c. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

         AND
      ii. The requested quantity (dose) is greater than the FDA labeled dose

         AND

iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval:

Promacta	ITP	2 months
	Thrombocytopenia in Hep C	3 months
	Severe aplastic anemia	4 months
	Another FDA approved diagnosis	12 months
Tavalisse	ITP	4 months

Renewal Evaluation
Promacta® or **Tavalisse™** will be renewed when the following are met:

1. The patient has been previously approved for therapy through Prime Therapeutics PA process.
   AND
2. The patient does not have any FDA labeled contraindications to therapy
   AND
3. ONE of the following:
   a. The patient has the diagnosis of chronic immune (idiopathic) thrombocytopenia and ONE of the following:
      i. The patient's platelet count is ≥50 x 10^9/L
         OR
      ii. The patient's platelet count has increased sufficiently to avoid clinically important bleeding

   OR

   b. The patient has the diagnosis of hepatitis C associated thrombocytopenia and BOTH of the following:
      i. ONE of the following:
         1. The patient will be initiating hepatitis C therapy with pegylated interferon and ribavirin
            OR
         2. The patient will be maintaining hepatitis C therapy with pegylated interferon and ribavirin at the same time as Promacta (eltrombopag)

      AND

      ii. ONE of the following:
         1. The patients platelet count is ≥90 x 10^9/L
            OR
         2. The patients platelet count has increased sufficiently to initiate or maintain interferon based therapy for the treatment of hepatitis C

   OR

   c. The patient has the diagnosis of severe aplastic anemia and has had a hematological response by week 16 defined as ONE of the following:
      i. Platelet count increases to 20 x 10^9/L above baseline
         OR
      ii. Stable platelet counts with transfusion independence for a minimum of 8 weeks
         OR
      iii. Hemoglobin increase by greater than 1.5 g/dL
         OR
      iv. Reduction in greater than or equal to 4 units of Red Blood Cell (RBC) transfusions for 8 consecutive weeks

OR

v. An Absolute Neutrophil Count (ANC) increase of 100%

OR

vi. An Absolute Neutrophil Count (ANC) increase greater than 0.5 x 10^9/L

AND

4. ONE of the following:
    a. The quantity (dose) requested is less than or equal to the program quantity limit

    OR

    b. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit

        AND

        ii. The requested quantity (dose) is less than or equal to the FDA labeled dose

        AND

        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit.

    OR

    c. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit

        AND

        ii. The requested quantity (dose) is greater than the FDA labeled dose

        AND

        iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of approval: 12 months for ITP and severe aplastic anemia. 48 weeks for HCV genotype 1,4,6 and 24 weeks for HCV genotype 2,3.

FDA APPROVED INDICATIONS AND DOSAGE[1,2,16]

Agent	Indication	Dosing
Promacta (eltrombopag)	For the treatment of 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.	Initiate 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. Discontinue Promacta for ITP if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum daily dose of 75 mg.
	For the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy	Initiate at 25 mg once daily for all patients. Adjust by 25 mg increments every 2 weeks as necessary to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. Discontinue Promacta when antiviral therapy is discontinued
	For the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy	Initiate 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. It may take up to 16 weeks for dose titration.

Limitation of Use:

- Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk of bleeding. It should not be used in an attempt to normalize platelet counts.
- Promacta should be used only 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.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

Agent	Indication	Dosing
Nplate (romiplostim)	Treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.	Initial dose of 1 mcg/kg once weekly as a subcutaneous injection. Adjust weekly dose by increments of 1 mcg/kg to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelet count is > 400 x 10^9/L. Discontinue romiplostim if platelet count does not increase after 4 weeks at the maximum dose. After platelet count has fallen to ≤ 200 x 10^9/L, resume romiplostim at a dose reduced by 1 mcg/kg.
Tavalisse	Treatment of thrombocytopenia in	100 mg orally twice daily. After a month, if platelet

(fostamatinib disodioum hexahydrate)	adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment	count has not increased to at least 50 X 10^9/L, increase dose to 150 mg twice daily

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts

CLINICAL RATIONALE

Chronic Idiopathic Thrombocytic Purpura

The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count.[8] The decision to treat involves consideration of the severity of bleeding, anticipated surgical procedure, medication side effects, and health-related quality of life. The majority of patients with no bleeding or mild bleeding can be treated with observation alone regardless of platelet count.[8] Severe bleeding typically does not occur unless a platelet count is <10,000-20,000/microL. A platelet count of 30,000/microL provides a safety margin and allows for fluctuations in levels. Treatment may be needed for platelet counts >30,000/microL when the patient is at an increased risk for bleeding (e.g. peptic ulcer disease, high risk for falling) or due to lifestyle (e.g. active sports) or occupation.[15] An International Working Group consensus panel defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3-12 months from diagnosis), or chronic (lasting for more than 12 months).[8]

NICE guidelines issued in 2011 and updated in 2014 recommend romiplostim as an option for treating adults with chronic ITP in adults who have had a splenectomy and whose condition is refractory to other treatments, or as second-line treatment in adults who have not had a splenectomy because surgery is contraindicated. These guidelines also state that romiplostim should only be recommended to patients if their condition is refractory to standard treatments and rescue therapies, or if they have severe disease with a high risk of bleeding requiring frequent courses of rescue therapies.[9] NICE guidance (2013) for the use of eltrombopag recommend its use as an option for treating adults who have had a splenectomy and whose condition is refractory to other treatments (e.g. corticosteroids or immunoglobulins) or as second line treatment in adults who have a contraindication to splenectomy only if their condition is refractory to standard active treatments and rescue therapies or they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.[10]

Eltrombopag and romiplostim have shown efficacy in RCTs in splenectomized or nonsplenectomized patients with persistent or chronic thrombocytopenia. The American Society of Hematology (ASH) ITP guidelines recommend thrombopoietin receptor agonists for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy [i.e. first-line treatment options include observation, corticosteroids, IVIg or anti-D immunoglobulin(anti-D)].[8] These agents may also be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not undergone splenectomy. The guidelines do not prefer one agent over the other. UpToDate suggests splenectomy (provided the patient can tolerate surgery) after failure to initial therapy with glucocorticoids and states that TPO receptor agonists should be reserved for patients who are unable to tolerate a splenectomy and/or rituximab.[15]

Eltrombopag and romiplostim have not been approved to increase platelet counts in disease states other than ITP.

Chronic Hepatitis C associated thrombocytopenia
Safety and efficacy was evaluated in 2 randomized, double-blind, placebo-controlled trials for eltrombopag in treating thrombocytopenia in patients with chronic hepatitis C. One trial used peginterferon alfa-2a (Pegasys); the other used peginterferon alfa-2b (Pegintron), both were in combination with ribavirin. Approximately 30% of patients had been previously treated with interferon and ribavirin. Patients had to have platelet counts of $<75 \times 10^9$/L. The trials consisted of 2 phases: a pre-antiviral treatment phase and an antiviral treatment phase. Patients were allowed to be randomized for the antiviral treatment phase if they reached the platelet count threshold of $\geq 90 \times 10^9$/L (trial 1) and $\geq 100 \times 10^9$/L (trial 2). The maximum allowed time on open label eltrombopag was 9 weeks. The primary efficacy endpoint for both studies was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count in study 1 was approximately 2 weeks with 95% of patients initiating antiviral therapy.

Severe Aplastic Anemia
The International Aplastic Anemia Study Group (IAASG) [also echoed by the General Haematology Task Force of the British Committee for Standards in Haematology and British Committee for Standards in Haematology] define severe aplastic anemia as including at least 2 of the 3 following blood criteria and either marrow criteria:[12,14]

IAASG staging criteria for blood:
- Neutrophils less than 0.5×10^9/L
- Platelets less than 20×10^9/L
- Reticulocytes less than 1% corrected (percentage of actual hematocrit [Hct] to normal Hct) or reticulocyte count $<20 \times 10^9$/L

IAASG staging criteria for marrow:
- Severe hypocellularity: <25%
- Moderate hypocellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells

The standard treatment for aplastic anemia is immunosuppressive therapy with horse antithymocyte globulin (ATG) and cyclosporine, and hematologic responses are observed in about two thirds of patients. Patients with disease that is refractory to immunosuppression and those who have a relapse after treatment may undergo allogeneic hematopoietic stem-cell transplantation (HSCT). However, 20 to 40% of patients without a suitable donor for HSCT continue to have severe cytopenias and are at risk for life-threatening hemorrhage due to thrombocytopenia and severe infections due to neutropenia. No standard therapies are available for patients who have aplastic anemia that is refractory to immunosuppression and are ineligible for HSCT, other than transfusions and treatment of infections. More than 40% of patients with disease that is refractory to immunosuppression die from bleeding or infection within 5 years after diagnosis. Although readministration of immunosuppressive therapy has been effective as salvage therapy in some patients, intensification of the regimen with more potent agents, such as rabbit ATG, sirolimus, or mycophenolate, has not improved the response rate.[11,13]

REFERENCES

1. Nplate prescribing information. Amgen. April 2016.
2. Promacta prescribing information. Novartis. October 2016.
3. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double blind randomized controlled trial. *Lancet* 2008;371:395-403.

4. Bussel JB*, Chen*g G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;357:2237-2247.
5. GlaxoSmithKline. Promacta Managed Care Dossier. 2008.
6. Gernsheimer TB, George JN, Aledort LM, et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). *J Thromb Haemost* 2010; 8 (6): 1372-82. [Abstract only]
7. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immun. thrombocytopenia. *NEJM* 2010; 363: 1889-99.
8. 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.
9. National Institute for Health and Care Excellence (2014): Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. Accessed 2/13/17.
10. NICE Guidance. July 2013. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). Accessed 2/13/17.
11. Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia. N Engl J Med 2012; 367:11-19July 5, 2012DOI: 10.1056/NEJMoa1200931. http://www.nejm.org/doi/full/10.1056/NEJMoa1200931#t=articleTop. Accessed 02/13/17.
12. http://emedicine.medscape.com/article/198759-workup#aw2aab6b5b5. Accessed 02/13/17.
13. http://www.nejm.org/doi/full/10.1056/NEJMoa1103975. Horse versus Rabbit Antithymocyte Globulin in Acquired Aplastic Anemia. Accessed 02/13/17.
14. British Society for Haematology. http://www.bcshguidelines.com/documents/Aplast_anaem_bjh_june2010.pdf. Accessed 02/13/2017.
15. UpToDate. Immune thrombocytopenia (ITP) in adults: Initial treatment and prognosis.; Second-line and subsequent therapies. Accessed 2/13/17.
16. Tavalisse prescribing information. Rigel Pharmaceuticals, Inc. April 2018.