This program applies to Medicaid formularies.

Nplate is not a target in this program.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doptelet®</strong></td>
<td>• Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>Patients with chronic liver disease: Platelet count less than 40 x 10⁹/L: 60 mg (3 tablets) orally once daily for 5 days</td>
</tr>
<tr>
<td><strong>(avatrombopag)</strong></td>
<td>• Thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to previous therapy</td>
<td>Platelet count 40 to less than 50 x 10⁹/L: 40 mg (2 tablets) orally once daily for 5 days</td>
</tr>
<tr>
<td><strong>Mulpleta®</strong></td>
<td>• Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>Chronic immune thrombocytopenia: Begin Doptelet at a starting dose of 20 mg daily. After initiating therapy with Doptelet, assess platelet counts weekly until a stable platelet count of 50 x 10⁹/L has been achieved, and then obtain platelet counts monthly thereafter. Dose adjustments are based on platelet counts (see prescribing information for information). Do not exceed a daily dose of 40 mg (2 tablets)</td>
</tr>
<tr>
<td><strong>(lusutrombopag)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nplate®</strong></td>
<td>• Treatment of thrombocytopenia in adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • Treatment of immune thrombocytopenia (ITP) in pediatric patients 1 year of age and older with</td>
<td>Patients with chronic liver disease: 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 10⁹/L as necessary to reduce the risk for bleeding.</td>
</tr>
<tr>
<td><strong>(romiplostim)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subcutaneous injection</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Promacta**<sup>®</sup> (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. Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.  

- **Chronic ITP:**  
  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<sup>9</sup>/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.  

- **Chronic Hepatitis C-associated Thrombocytopenia:**  
  Initiate 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.  

- **First-line therapy for severe aplastic anemia:**  
  Patients 12 years and older:  
  150 mg once daily for 6 months |  

|  | ITP for at least 6 months, who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy  

Limitations of Use:  
- **Nplate** is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than 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.

- Do not exceed the maximum weekly dose of 10 mcg/kg.  
- Do not dose if platelet count is > 400 x 10<sup>9</sup>/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<sup>9</sup>/L, resume romiplostim at a dose reduced by 1 mcg/kg. |
For the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy

Limitations 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.

**Pediatric patients 6 to 11 years:**
75 mg once daily for 6 months

**Pediatric patients 2 to 5 years:**
2.5 mg/kg once daily for 6 months

- Severe Aplastic Anemia after 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 10⁹/L. Do not exceed 150 mg per day.

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**Tavalisse™**
(fostamatinib disodium hexahydrate)

Oral tablet

- Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment

- 100 mg orally twice daily. After a month, if platelet count has not increased to at least 50 X 10⁹/L, increase dose to 150 mg twice daily

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**CLINICAL RATIONALE**

**Immune (Idiopathic) Thrombocytopenia**

Immune (idiopathic) thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by a low platelet count resulting from platelet destruction and impaired platelet production. ITP can be an isolated primary condition, or it may be secondary to other conditions. 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. Bleeding events are often unpredictable and patients with ITP, even in the setting of severe thrombocytopenia, may not exhibit bleeding beyond bruising and petechiae. However, more serious mucosal bleeding may occur, including menorrhagia, epistaxis, gastrointestinal hemorrhage, hematuria, or, rarely, intra-cranial hemorrhage. The decision as to whether a patient can be observed or requires further intervention is highly complex and varies based on comorbidities, medications, and age, which all impact the risk of bleeding. In addition, management approaches may vary...
based on disease duration, access to care, quality-of-life implications, and patient and provider preferences, among other factors. 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).\(^6\)

National Institute for Health and Care Excellence (NICE) guidelines issued in 2011 and updated in 2014 recommend romiplostim as an option for treating adults with chronic ITP 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.\(^7\)

The American Society of Hematology (ASH) 2019 guidelines for immune thrombocytopenia separate treatments into adult and pediatric categories as well as initial vs secondary treatments in both groups.

In adults with newly diagnosed ITP and a platelet count of \(< 30 \times 10^9/L\) who are asymptomatic or have minor mucocutaneous bleeding, ASH suggests corticosteroids rather than management with observation. There may be a subset of patients within this group for whom observation might be appropriate. This should include consideration of the severity of thrombocytopenia, additional comorbidities, use of anticoagulant or antiplatelet medications, need for upcoming procedures, and age of the patient.\(^6\)

In adults with newly diagnosed ITP and a platelet count \(\geq 30 \times 10^9/L\) who are asymptomatic or have minor mucocutaneous bleeding, the ASH panel recommends against corticosteroids and in favor of management with observation. For patients with a platelet count at the lower end of this threshold, for those with additional comorbidities, anticoagulant or antiplatelet medications, or upcoming procedure, and for elderly (> 60 years old), treatment with corticosteroids may be appropriate.\(^6\)

In adult patients with ITP for \(\geq 3\) months who are corticosteroid dependent or do not have a response to corticosteroids, the ASH panel suggests treatment with a thrombopoietin receptor agonist (the guidelines suggest either eltrombopag or romiplostim but also acknowledge no therapies available after 2017 were included in these guidelines), rituximab, or a splenectomy. The panel suggests use of a thrombopoietin receptor agonist over rituximab or a splenectomy and rituximab over a splenectomy. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of patient, medication adherence, medical and social support networks, patient values and preferences, cost, and availability.\(^6\)

In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished health related quality of life (HRQoL), the panel suggests corticosteroids over IVIG or anti-D immunoglobulin but does suggest that IVIG or anti-D immunoglobulin could be used in certain situations.\(^6\)

In children with ITP who have non-life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment the ASH panel suggests the use of thrombopoietin receptor agonists over rituximab or splenectomy and rituximab over splenectomy.\(^6\)

Given the impact of corticosteroids on mental health, the treating prescriber should assess HRQoL (e.g., depression, fatigue, mental status) while patients are receiving corticosteroids. Based on clinical experience, the ASH panel agreed there was likely trivial benefit in continuing corticosteroids in adults beyond 6 weeks. For the majority of patients, a trial of 6 weeks of
corticosteroids should determine whether a patient is going to enter remission or will require additional therapy. For patients who require additional therapy, consideration of alternative therapy is preferred over ongoing exposure to corticosteroids. In children the ASH panel advises against courses of corticosteroids longer than 7 days.6

Recommendations from the 2011 ASH guidelines that were not prioritized to be addressed, discussed or updated by the 2019 guideline panel were as follows:6

- First-line treatment of adult ITP:
  - IVIG with corticosteroids can be used when a more rapid increase in platelet count is required
  - Either IVIG or anti-D (in appropriate patients) can be used as a first-line treatment if corticosteroids are contraindicated

Chronic Hepatitis C associated thrombocytopenia11
A number of studies have suggested an association between hepatitis C virus (HCV) infection and immune thrombocytopenia (ITP) and/or autoimmune hemolytic anemia, either as a consequence of interferon therapy or in the setting of chronic infection without therapy. One of the largest studies included 120,691 United States veterans with chronic HCV who were matched with 454,905 controls. HCV was associated with ITP in both treated and untreated patients (hazard ratio 1.8).

Severe Aplastic Anemia
The British Journal of Haematology guidelines for the diagnosis and management of adult aplastic anaemia define severe aplastic anemia as:10

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

AND
1 of the following marrow criteria:
- 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.6,9

Thrombocytopenia in liver disease12
Patients with acute and chronic liver disease frequently acquire unique changes in hemodynamic and hemostatic pathways that may result in life-threatening bleeding and thrombosis. Additionally, activation of hemostatic pathways may play a role in disease
progression through prechymal extinction, or organ atrophy, recruitment of inflammatory cells and activation of stellate cells.

Traditional coagulation measures, including pro-thrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and bleeding time (BT) do not measure bleeding risk in cirrhosis. In addition, platelet count alone provides an incomplete guide to bleeding risk in cirrhosis. However, values below 50,000/µL may be associated with a higher risk of bleeding.

Procedure-related bleeding is common in cirrhosis patients but estimates of incidence vary widely. For many years, the PT/INR served as a surrogate marker for estimating bleeding risk in cirrhosis. However, use of INR and arbitrary “cut-offs” as a clinical target is not recommended or supported by scientific evidence. Assessment of individual patient characteristics is also essential as clinical factors, such as acute kidney injury or infection may alter bleeding risk in certain clinical scenarios. In elective and planned settings, such as planned dental extractions or other invasive procedures with moderate or high risk, thrombopoietin receptor agonists are an alternative means to increase platelets prior to invasive procedures.

**Efficacy**

**Doptelet**

Doptelet (avatrombopag) is a thrombopoietin receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased production of platelets.

The efficacy of Doptelet for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 and ADAPT-2). In each study, patients were assigned to the low baseline platelet count cohort (<40 X 10⁹ L) or high baseline platelet count cohort (≥ 40 to < 50 X 10⁹ L) based on their platelet count at baseline.

In the ADAPT-1 trial 149 patients were treated with Doptelet and 82 patients were treated with placebo both once daily for 5 days. In the ADAPT-2 trial, 128 patients were treated with Doptelet and 76 patients were treated with placebo. Across both baseline platelet count cohorts and the Doptelet and placebo treatment groups, patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk.

The major efficacy outcome in both trials was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Additional secondary efficacy outcomes were the proportion of patients who achieved platelet counts of ≥ 50 X 10⁹ L on the day of procedure and the change in platelet count from baseline to procedure day.

Responders were defined as patients who did not require a platelet transfusion or any rescue procedure (whole blood transfusion, packed red blood cell transfusion, platelet transfusion, fresh frozen plasma or cryoprecipitate administration, Vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, or surgical or interventional radiology performed to achieve hemostasis and control blood loss) for bleeding after randomization and up to 7 days following a scheduled procedure. In both baseline platelet count cohorts, patients in the Doptelet treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant.
The percentage of responders in the low baseline platelet count cohort and treatment group that responded in the ADAPT-1 trial was 66% in the Doptelet group and 23% in the placebo group (p-value <0.0001). In the ADAPT-2 trial the percentage of responders was 69% in the Doptelet group and 35% in the placebo group (p-value 0.0006).

The percentage of responders in the high baseline platelet count cohort in ADAPT-1 trial was 88% in the Doptelet group and 38% in the placebo group (p-value <0.0001). In the ADAPT-2 trial the percentage of responders was 88% in the Doptelet group and 33% in the placebo group (p-value <0.0001).

Both trials also demonstrated a higher proportion of patients who achieved the target platelet count of ≥ 50 X 10^9/L on the day of the procedure (a secondary efficacy endpoint) and a greater mean change in platelet counts from baseline to the day of the procedure (a secondary efficacy endpoint).

The efficacy of Doptelet in adult patients with chronic immune thrombocytopenia was evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT01438840). Patients had received one or more chronic immune thrombocytopenia therapies and had an average platelet count of 30 X 10^9/L. The major efficacy outcome was the cumulative number of weeks in which the platelet count was ≥ 50 X 10^9/L during the 6-month treatment period in the absence of rescue therapy. Doptelet-treated patients had a longer duration of platelet counts ≥50 x10^9/L in the absence of rescue therapy than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, p<0.0001. In addition, a larger proportion of patients in the Doptelet treatment group had platelet counts ≥ 50 X 10^9/L at Day 8 compared to placebo (21/32; 66% vs 0/17; 0.0%, respectively; p<0.0001).

Mulpleta^2
Mulpleta (lusutrombopag) is an orally bioavailable TPO receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation.

The efficacy of Mulpleta for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was evaluated in 2 randomized, double-blind, placebo-controlled trial (L-PLUS 1 and L-PLUS 2). Patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50 X 10^9/L were eligible to participate. Patients were randomized to receive 3 mg of Mulpleta or placebo once daily for up to 7 days.

In L-PLUS 1 the major efficacy outcome was the proportion of patients who require no platelet transfusion prior to the primary invasive procedure. In L-PLUS 2 the major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding (i.e., platelet preparations, other blood preparations, including red blood cells and plasma, volume expanders) from randomization through 7 days after the primary invasive procedure. In both the L-PLUS 1 and L-PLUS 2 trials, responders were defined as patients who had a platelet count of ≥ 50 X 10^9/L with an increase of ≥ 20 X 10^9/L from baseline.

In the L-PLUS 1 trial the percentage of patients not requiring platelet transfusion prior to invasive procedure was 78% in the Mulpleta arm and 13% in the placebo arm (95% CI, P-value <0.0001). The percentage of patients that responded during the study was 76% in the Mulpleta arm and 6% in the placebo arm (95%CI, p-value <0.001).
In the L-Plus 2 trial the percentage of patients not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding from randomization through 7 days after invasive procedure was 65% in the Mulpleta arm and 29% in the placebo arm (95% CI, P-value <0.0001). The percentage of patients that responded during the study was 65% in the Mulpleta arm and 13% in the placebo arm (95% CI, p-value <0.001).

**Nplate**

Nplate (romiplostim) is a thrombopoietin receptor agonist that increases platelet production through binding and activation of the thrombopoietin (TPO) receptor, similar in mechanism to endogenous TPO.

The safety and efficacy of Nplate were assessed in two double-blind, placebo-controlled clinical studies, in an open-label single-arm study, and in an open-label extension study. Efficacy in all studies was defined as maintaining a target platelet count ≥ 50 X 10^9/L.

The safety and efficacy of Nplate in pediatric patients 1 year and older with ITP for at least 6 months were assessed in two double-blind, placebo controlled clinical trials. The efficacy in both studies was defined as maintaining a target platelet count of ≥ 50 X 10^9/L.

**Promacta**

Promacta (eltrombopag) interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production.

Safety and efficacy of Promacta in adult patient with chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial. Safety and efficacy of Promacta in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. All of these trials showed clinically significant efficacy of Promacta vs placebo.

Safety and efficacy of Promacta 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 (Peginteron), 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 x10^9/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 ≥ 90 X 10^9/L (trial 1) and ≥100 X 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.

The safety of Promacta as first-line treatment of severe aplastic anemia was established based on a single-arm trial of 153 patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy. In this trial, Promacta was administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine. The efficacy of Promacta in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) >1,000/μL, platelet count > 100 X 10^9/L, and hemoglobin > 10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC > 500/μL, platelet count > 20 X 10^9/L, or
reticulocyte count > 60,000/μL. Overall response rate is defined as the number of partial responses plus complete responses. The overall response rate at month 6 was 79% (95% CI). The median duration of overall response was 70 months (95% CI). The median duration of complete response was 46 months (95% CI).

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 of less than or equal to 30 X 10⁹/L. 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 10⁹/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 greater than or equal to 4 units of red blood cell transfusions for 8 consecutive weeks; 3) ANC increase of 100% or an ANC increase greater than or equal to 0.5 X 10⁹/L. Promacta was discontinued after 16 weeks if no hematologic response was observed. The response rate was 40% (95% CI) and the median of duration of response was not reached due to few events.

Tavalisse⁵

Tavalisse (fostamatinib) is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase.

Tavalisse was studied in two placebo-controlled efficacy and safety studies (FIT-1 and FIT-2), and an open-label extension study (FIT-3).

A total of 150 patients with persistent or chronic immune thrombocytopenia, who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonists) were enrolled in two identical, double-blind, placebo-controlled studies that were conducted in different countries. For each study, patients were randomized to receiving Tavalisse or placebo for 24 weeks. Patients who did not respond to treatment after 12 weeks, as well as patients who completed the 24-week double-blind study, were eligible to enroll in the open-label extension study. The efficacy of Tavalisse was based on stable platelet response (at least 50 X 10⁹/L on at least 4 of the 6 visits between weeks 14 to 24).

The percent of patients who had a stable platelet response was 16-18% in the Tavalisse arms and 0-1% in the placebo arms.

The FIT-3 extension study enrolled 123 patients who completed 24 weeks of treatment in the FIT-1 and FIT-2 studies, or who did not respond to treatment any time after 12 weeks in these studies. Patients who were designated as responders in the FIT-1 and FIT-2 studies (defined as platelet count of at least 50 X 10⁹/L) at the time of rollover continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders (defined as platelet count less than 50 X 10⁹/L) received Tavalisse 100 mg twice daily regardless of their dose and regimen in the prior study. Stable response in this study was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count less than 50 X 10⁹/L, without an intervening visit with a platelet count of at least 50 X 10⁹/L (unrelated to rescue therapy), within a period of 12 weeks following initial achievement of the target platelet count.

Among the patients who achieved stable response in FIT-1, FIT-2, and FIT-3 trials, 18 patients maintained the platelet count of at least 50 X 10⁹/L for 12 months or longer.

REFERENCES

Thrombopoietin Receptor Agonists Prior Authorization with Quantity Limit

TARGET AGENTS
Doptelet® (avatrombopag)
Mulpleta® (lusutrombopag)
Nplate® (romiplostim)
Promacta® (eltrombopag)
Tavalisse™ (fostamatinib disodium)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>Doptelet (avatrombopag) oral tablet</td>
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<td>M, N, O, or Y</td>
<td>2 tablets/day</td>
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<td>20 mg tablet</td>
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<td>Nplate (romiplostim) subcutaneous injection</td>
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PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation
The target agents will be approved when the ALL of the following are met:
1. ONE of the following:
   A. The requested agent is Doptelet AND ONE of the following:
      i. The patient has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP) AND ALL of the following:
         1. ONE of the following:
            a. The patient has a platelet count ≤ 30 X 10^9/L
               OR
            b. The patient has a platelet count > 30 X 10^9/L but < 50 X 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding
      AND
   2. ONE of the following:
a. The patient has tried and had an inadequate response to corticosteroids

OR

b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to corticosteroids

OR

c. The patient has tried and had an inadequate response to another thrombopoietin receptor agonist (e.g., Mulpleta, Nplate, Promacta, Tavalisse)

OR

d. The patient has tried and had an inadequate response to immunoglobulins (IVIg or Anti-D)

OR

e. The patient has had an inadequate response to a splenectomy

OR

ii. The patient has a diagnosis of thrombocytopenia and has chronic liver disease AND ALL of the following:
   1. The patient has a platelet count < 50 x 10⁹/L
      AND
   2. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure)
      AND
   3. The patient would require a platelet transfusion unless platelet counts are clinically increased from baseline

OR

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

OR

B. The requested agent is Mulpleta (lusutrombopag) AND ONE of the following:
   i. The patient has a diagnosis of thrombocytopenia and has chronic liver disease AND BOTH of the following:
      1. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure)
      AND
      2. The patient would require a platelet transfusion unless platelet counts are clinically increased from baseline

OR

ii. The patient has another FDA approved diagnosis for the requested agent

OR

C. The requested agent is Nplate (romiplostim) AND ONE of the following:
   i. The patient has a diagnosis of immune (idiopathic) thrombocytopenia (ITP) AND ALL of the following:
      1. ONE of the following:
         a. The patient is between the ages of 1 and 17 years old AND the diagnosis has lasted for at least 6 months
         OR
         b. The patient is 18 years old or over
         AND
      2. ONE of the following:
         a. The patient has a platelet count ≤ 30 x 10⁹/L
         OR
      a. The patient has a platelet count ≤ 30 x 10⁹/L
      OR
b. The patient has a platelet count > 30 \times 10^9/L but < 50 \times 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding

AND

3. ONE of the following:
   a. The patient has had an inadequate response to corticosteroids
   OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to corticosteroids
   OR
   c. The patient has tried and had an inadequate response to immunoglobulins (IVIg or anti-D)
   OR
   d. The patient has had an inadequate response to a splenectomy

OR

ii. The patient has another FDA approved diagnosis for the requested agent

OR

D. The requested agent is Promacta (eltrombopag) AND ONE of the following:
   i. The patient has a diagnosis of hepatitis C associated thrombocytopenia AND ONE of the following:
      1. The intent of therapy with the requested agent is to increase platelet counts sufficiently to initiate pegylated interferon therapy AND the patient’s platelet count is < 75 \times 10^9/L
      OR
      2. The patient is on concurrent therapy with a pegylated interferon and ribavirin AND is at risk for discontinuing hepatitis C therapy due to thrombocytopenia

OR

ii. The patient has a diagnosis of severe aplastic anemia AND ALL of the following:
   1. The patient has at least 2 of the following blood criteria:
      a. Neutrophils less than 0.5 \times 10^9/L
      b. Platelets less than 20 \times 10^9/L
      c. Reticulocytes less than 1% corrected [percentage of actual hematocrit (Hct) to normal Hct] or reticulocyte count < 20 \times 10^9/L

   AND

   2. The patient has 1 of the following marrow criteria:
      a. Severe hypopcellularity: <25%
      OR
      b. Moderate hypopcellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells

   AND

   3. ONE of the following:
      a. BOTH of the following:
         i. The patient will use the requested agent as first-line treatment
         AND
         ii. The patient will use the requested agent in combination with standard immunosuppressive therapy [i.e. antithymocyte globulin (ATG) AND cyclosporine]
OR
b. ONE of the following:
   i. The patient has tried and had an inadequate response to BOTH antithymocyte globulin (ATG) AND cyclosporine therapy
   OR
   ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH ATG AND cyclosporine

OR
iii. The patient has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP) AND BOTH of the following:
   1. ONE of the following:
      a. The patient has a platelet count ≤ 30 x 10^9/L
      OR
      b. The patient has a platelet count > 30 x 10^9/L but < 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding

   AND
   2. ONE of the following:
      a. The patient has tried and had an inadequate response to corticosteroids
      OR
      b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to corticosteroids
      OR
      c. The patient has tried and had an inadequate response to immunoglobulins (IVIg or anti-D)
      OR
      d. The patient has had an inadequate response to a splenectomy

OR
iv. The patient has another FDA labeled indication for the requested agent

OR
E. The requested agent is Tavalisse (fostamatinib disodium hexahydrate) AND ONE of the following:
   i. The patient has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP) AND ALL of the following:
      1. ONE of the following:
         a. The patient has a platelet count ≤ 30 X 10^9/L
         OR
         b. The patient has a platelet count > 30 X 10^9/L but < 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding

      AND
      2. ONE of the following:
         c. The patient has tried and had an inadequate response to corticosteroids
         OR
         d. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to corticosteroids
         OR
e. The patient has tried and had an inadequate response to another thrombopoietin receptor agonist (e.g., Mulpleta, Nplate, Promacta, Tavalisse)
   **OR**

f. The patient has tried and had an inadequate response to immunoglobulins (IVIg or Anti-D)
   **OR**

g. The patient has had an inadequate response to a splenectomy
   **OR**

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

**AND**

2. The patient will NOT use the requested agent in combination with another thrombopoietin receptor agonist agent included in this program

**AND**

3. The patient does NOT have any FDA labeled contraindications to the requested agent

**AND**

4. **ONE of the following:**
   A. The requested quantity (dose) does not exceed 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) does not exceed the maximum FDA labeled dose for the requested indication
      **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 maximum FDA labeled dose for the requested indication
      **AND**

      iii. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

**Initial Lengths of Approval:**

<table>
<thead>
<tr>
<th><strong>Doptelet</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ITP</td>
<td>6 months</td>
</tr>
<tr>
<td>Thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>1 month</td>
</tr>
<tr>
<td>Another FDA approved indication</td>
<td>6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mulpleta</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>1 month</td>
</tr>
<tr>
<td>Another FDA approved indication</td>
<td>6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Promacta</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ITP</td>
<td>2 months</td>
</tr>
</tbody>
</table>
Renewal Evaluation

The targeted agent will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process. *note Doptelet for thrombocytopenia with chronic liver disease and Multpleta should always be reviewed under initial criteria

   AND

2. ONE of the following:
   A. The patient has a diagnosis of immune (idiopathic) thrombocytopenia (ITP) AND ONE of the following:
      i. The patient’s platelet count is $\geq 50 \times 10^9/L$
      OR
      ii. The patient’s platelet count has increased sufficiently to avoid clinically significant 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
      AND
      ii. ONE of the following:
         1. The patient’s platelet count is $\geq 90 \times 10^9/L$
         OR
         2. The patient’s platelet count has increased sufficiently to initiate or maintain pegylated interferon based therapy for the treatment of hepatitis C
   OR
   C. The patient has the diagnosis of severe aplastic anemia AND ONE of the following:
      i. BOTH of the following:
         1. The patient will use the requested agent in combination with standard immunosuppressive therapy (i.e., antithymocyte globulin (ATG) and cyclosporine) for the first-line treatment of severe aplastic anemia
         AND
         2. The patient has had a response by 6 months defined as meeting TWO of the following values on 2 consecutive serial blood count measurements at least 1 week apart:
i. An absolute neutrophil count (ANC) greater than 500/mcL
   OR
ii. Platelet count greater than 20 x 10⁹/L
   OR
iii. Reticulocyte count greater than 60,000/mcL

OR

ii. The patient will NOT use the requested agent in combination with standard immunosuppressive therapy AND has had a hematological response by week 16 defined as ONE of the following:
   1. Platelet count increased at least 20 x 10⁹/L above baseline
   OR
   2. Stable platelet counts with transfusion independence for a minimum of 8 weeks
   OR
   3. Hemoglobin increased by greater than 1.5 g/dL
   OR
   4. Reduction in greater than or equal to 4 units of Red Blood Cell (RBC) transfusions for 8 consecutive weeks
   OR
   5. An Absolute Neutrophil Count (ANC) increase of 100%
   OR
   6. An Absolute Neutrophil Count (ANC) increase greater than 0.5 x 10⁹/L

OR

D. The patient has another FDA approved indication for the requested agent AND has shown clinical improvement (i.e., decreased symptom severity and/or frequency)

AND

3. The patient will NOT use the requested agent in combination with another thrombopoietin receptor agonist agent included in this program

AND

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. ONE of the following:
   A. The requested quantity (dose) does not exceed 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) does not exceed the maximum FDA labeled dose for the requested indication
      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 maximum FDA labeled dose for the requested indication
      AND
iii. The prescriber has submitted information in support of therapy with a higher dose for the intended diagnosis

**Renewal Lengths of approval:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Length of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITP</td>
<td>12 months</td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>12 months</td>
</tr>
<tr>
<td>Another FDA approved indication for the requested agent</td>
<td>12 months</td>
</tr>
<tr>
<td>Thrombocytopenia in hepatitis C</td>
<td>6 months</td>
</tr>
</tbody>
</table>

**FDA Labeled Contraindications**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doptelet® (avatrombopag)</td>
<td>None</td>
</tr>
<tr>
<td>Mufpleta® (lusutrombopag)</td>
<td>None</td>
</tr>
<tr>
<td>Nplate® (romiplostim)</td>
<td>None</td>
</tr>
<tr>
<td>Promacta® (eltrombopag)</td>
<td>None</td>
</tr>
<tr>
<td>Tavalisse™ (fostamatinib disodium hexahydrate)</td>
<td>None</td>
</tr>
</tbody>
</table>
Step Therapy Supplement Program Summary

This program applies to Medicaid.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      **AND**
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      **AND**
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   **OR**

2. BOTH of the following
   a. The patient’s medication history includes the required prerequisite/preferred agent(s) or a drug in the same pharmacological class with the same mechanism of action as indicated by ONE of the following:
      i. Evidence of a paid claim(s) within the past 999 days
      **OR**
      ii. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days
      **AND**
   b. ONE of the following:
      i. The required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
      **OR**
      ii. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over the prerequisite/preferred agent(s)

   **OR**

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria