### Thrombopoietin Receptor Agonists Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed Health Insurance Marketplace, FocusRx and KeyRx formularies.

Nplate is not a target in this program.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

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>
</table>
| **Doptelet®** (avatrombopag) | • Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure  
• Thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to previous therapy | **Patients with chronic liver disease:**  
Platelet count less than 40 x 10⁹/L:  
60 mg (3 tablets) orally once daily for 5 days  
Platelet count 40 to less than 50 x 10⁹/L:  
40 mg (2 tablets) orally once daily for 5 days  
**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) |
| **Mulpleta®** (lusutrombopag) | • Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure | **Patients with chronic liver disease:**  
3 mg (1 tablet) orally once daily for 7 days |
| **Nplate®** (romiplostim) | • 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 ITP for at least 6 months, who | **Immune thrombocytopenia:**  
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.  
Do not exceed the maximum weekly dose of 10 mcg/kg. |
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 dose if platelet count is > 400 x 10⁹/L.
Discontinue romiplostim if platelet count does not increase after 4 weeks at the maximum dose. After platelet count has fallen to ≤ 200 x 10⁹/L, resume romiplostim at a dose reduced by 1 mcg/kg.

Promacta®
(eltrombopag)

Oral tablet
Powder for oral suspension

● 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 10⁹/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

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.

● In combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia

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

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

<table>
<thead>
<tr>
<th>Tavalisse™ (fostamatinib disodium hexahydrate) Oral tablet</th>
<th>Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment</th>
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<tbody>
<tr>
<td>Pediatric patients 2 to 5 years: 2.5 mg/kg once daily for 6 months</td>
<td></td>
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<tr>
<td><strong>Severe Aplastic Anemia after insufficient response to immunosuppressive therapy:</strong> 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.</td>
<td></td>
</tr>
</tbody>
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**CLINICAL RATIONALE**

**Chronic Immune (Idiopathic) Thrombocytopenia**

The goal of all treatment strategies for chronic immune (idiopathic) thrombocytopenia (ITP) is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count. 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. 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. 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).

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.\(^6\)

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)]. 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.\(^5\)

**Chronic Hepatitis C associated thrombocytopenia\(^{13}\)**

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:\(^{11}\)

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% corrected (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.\(^{8,10}\)

**Thrombocytopenia in liver disease\(^{14}\)**

It is generally accepted that liver disease leads to a form of "rebalanced" hemostasis, in which diminished hepatic function leads to both procoagulant and anticoagulant effects. All stages of the hemostatic process may be abnormal, including primary hemostasis (platelet adhesion and
activation), coagulation (generation and crosslinking of fibrin), and fibrinolysis (clot dissolution).

Factors that contribute to increased risks of both bleeding and thrombosis include altered blood flow, diminished numbers and function of platelets, and inflammatory alterations in endothelial cells. These changes may result in a relatively balanced steady state in some patients, but is generally accepted that susceptibility to bleeding and thrombosis both may be increased, with the relative balance or imbalance different for each patient.

Patients with liver disease may have normal platelet counts (i.e., ≥150,000/microL) or varying degrees of thrombocytopenia. Mild thrombocytopenia (e.g., platelet count between 100,000 and 150,000/microL) has been reported in up to 75 percent of patients with chronic liver disease, and moderate thrombocytopenia (e.g., between 50,000 and 100,000/microL) has been reported in approximately 13 percent of individuals with cirrhosis. The correlation between platelet count and clinical bleeding is weak, especially for counts >50,000/microL.

The mechanism of thrombocytopenia in liver disease may include impaired platelet production, from decreased hepatic synthesis of thrombopoietin; bone marrow suppression, from hepatitis C virus (HCV) infection or alcohol use, other infection, or antiviral or antibiotic therapy; and increased platelet sequestration in the spleen, in the setting of portal hypertension and hypersplenism.

**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 10^9L) or high baseline platelet count cohort (≥ 40 to < 50 X 10^9L) 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 10^9L 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

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 were 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.

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 placebo controlled studies included patients with immune thrombocytopenia who had at least one prior treatment and had a platelet count of ≤ 30 X 10^9/L. Prior treatments included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine.

The percentage of nonsplenectomized patients that had durable platelet response was 61% in the Nplate arm and 5% in the placebo arm. For splenectomized patients the percentage of patients that had durable platelet response was 38% in the Nplate arm and 0% in the placebo arm. The overall platelet response for nonsplenectomized patients was 88% in the Nplate arm and 14% in the placebo arm. For splenectomized patient the overall platelet response was 79% in the Nplate arm and 0% in the placebo arm.

Patients who participated in the placebo-controlled studies were withdrawn from study medication. If platelet counts subsequently decreased to ≤ 50 X 10^9/L, the patients were allowed to receive Nplate in an open-label extension study with weekly dosing based on platelet counts. In the 100 patients that entered the extension study, platelet counts were increased and sustained regardless of whether they received Nplate or placebo.

**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 clinical 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 (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 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 10^9/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 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase of 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 0.5 X 10^9/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.

Tavalisse

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 receive 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 10^9/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 10^9/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 10^9/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 10^9/L, without an intervening visit with a platelet count of at least 50 X 10^9/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 10^9/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>
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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:
   a. 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:
            a. ONE of the following:
               a. The patient has a platelet count ≤ 30 X 10⁹/L
               OR
               b. The patient has a platelet count > 30 X 10⁹/L but < 50 X 10⁹/L AND has symptomatic bleeding and/or an increased risk for bleeding
      AND
   b. ONE of the following:
a. The patient has had an insufficient response to a splenectomy

OR
b. The patient has tried and had an insufficient response to corticosteroids

OR
c. The patient has tried and had an insufficient response to immunoglobulins (IVIg or Anti-D)

OR
d. The patient has tried and had an insufficient response to another thrombopoietin receptor agonist (e.g., Nplate, Promacta)

OR
e. BOTH of the following:
   i. The patient is NOT a candidate for splenectomy
      AND
   ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH corticosteroids AND immunoglobulins (IVIg or Anti-D)

OR

ii. The patient has a diagnosis of thrombocytopenia and has chronic liver disease AND ALL of the following:
   a. The patient has a platelet count < 50 X 10^9/L
      AND
   b. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure)
      AND
   c. 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:
      a. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure)
      AND
   b. 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 has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP)

AND

2. ONE of the following:
   a. The patient has a platelet count ≤ 30 X 10⁹/L
   OR
   b. The patient has a platelet count > 30 X 10⁹/L but < 50 x 10⁹/L AND has symptomatic bleeding and/or an increased risk for bleeding

AND

3. ONE of the following:
   a. The patient has had an insufficient response to a splenectomy
   OR
   b. The patient has tried and had an insufficient response to corticosteroids or immunoglobulins (IVIg or anti-D)
   OR
   c. BOTH of the following:
      i. The patient is NOT a candidate for splenectomy
      AND
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH corticosteroids AND immunoglobulins (IVIg or Anti-D)

   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 x10⁹/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 X 10⁹/L
         b. Platelets less than 20 X 10⁹/L
         c. Reticulocytes less than 1% corrected [percentage of actual hematocrit (Hct) to normal Hct] or reticulocyte count < 20 X 10⁹/L
      AND
      2. The patient has 1 of the following marrow criteria:
         a. Severe hypocellularity: <25%
         OR
         b. Moderate hypocellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells
      AND
3. ONE of the following:
   i. BOTH of the following:
      i. The patient will be using 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
   ii. ONE of the following:
      i. The patient has tried and had an insufficient 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 10⁹/L
          OR
          b. The patient has a platelet count > 30 x 10⁹/L but < 50 x 10⁹/L AND has symptomatic bleeding and/or an increased risk for bleeding
       AND
       2. ONE of the following:
          a. The patient has had an insufficient response to a splenectomy
          OR
          b. The patient has tried and had an insufficient response to corticosteroids or immunoglobulins (IVIg or anti-D)
          OR
          c. BOTH of the following:
             i. The patient is NOT a candidate for splenectomy
             AND
             ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH corticosteroids AND immunoglobulins (IVIg or Anti-D)
   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 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

2. ONE of the following:
   a. The patient has had an insufficient response to a splenectomy
      OR
   b. The patient has tried and had an insufficient response to corticosteroids
      OR
   c. The patient has tried and had an insufficient response to immunoglobulins (IVIg or Anti-D)
      OR
   d. The patient has tried and had an insufficient response to another thrombopoietin receptor agonist (e.g., Nplate, Promacta)
      OR
   e. BOTH of the following:
      i. The patient is NOT a candidate for splenectomy
      AND
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH corticosteroids AND immunoglobulins (IVIg or Anti-D)
      OR
      ii. The patient has another FDA approved indication for the requested agent

AND

2. ONE of the following:
   A. The patient is NOT being treated with another thrombopoietin receptor agonist agent included in this program
   OR
   B. The patient is currently being treated with another thrombopoietin receptor agonist agent included in this program AND will discontinue prior to initiating the requested agent

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
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>Drug</th>
<th>Indication</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doptelet</td>
<td>ITP</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>1 month</td>
</tr>
<tr>
<td></td>
<td>Another FDA approved indication</td>
<td>6 months</td>
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<tr>
<td>Mulpleta</td>
<td>Thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>1 month</td>
</tr>
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<td>Another FDA approved indication</td>
<td>6 months</td>
</tr>
<tr>
<td>Promacta</td>
<td>ITP</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia in Hep C</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>First-Line therapy in severe aplastic anemia</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>All other severe aplastic anemia</td>
<td>4 months</td>
</tr>
<tr>
<td></td>
<td>Another FDA approved indication</td>
<td>6 months</td>
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<tr>
<td>Nplate</td>
<td>ITP</td>
<td>4 months</td>
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<td></td>
<td>Another FDA approved indication</td>
<td>6 months</td>
</tr>
<tr>
<td>Tavalisse</td>
<td>ITP</td>
<td>4 months</td>
</tr>
<tr>
<td></td>
<td>Another FDA approved indication</td>
<td>6 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 Mulpleta 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 ≥ 50 x 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 ≥ 90 x 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 is using 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. ONE of the following:
         a. The patient has had a complete response by 6 months defined as hematological parameters meeting ALL of the following values:
            i. An absolute neutrophil count (ANC) greater than 1,000/mcL
            **AND**
            ii. Platelet count greater than 100 x 10^9/L
            **AND**
            iii. Hemoglobin greater than 10 g/dL
         **OR**
         b. The patient has had a partial response by 6 months defined as meeting TWO of the following values:
            i. An absolute neutrophil count (ANC) greater than 500/mcL
            **OR**
            ii. Platelet count greater than 20 x 10^9/L
            **OR**
            iii. Reticulocyte count greater than 60,000/mcL
   **OR**
   ii. The patient is not using 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 increase at least 20 x 10^9/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 10^9/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. ONE of the following:
   A. The patient is NOT being treated with another thrombopoietin receptor agonist agent included in this program
   OR
   B. The patient is currently being treated with another thrombopoietin receptor agonist included in this program AND will discontinue prior to continuing the requested agent

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>
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<tr>
<th>Condition</th>
<th>Length</th>
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<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>
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

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. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days

OR

b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

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