ITP (Immune Thrombocytopenic Purpura)
Nplate® (romiplostim), Promacta® (eltrombopag)

Prior Authorization Criteria

FDA APPROVED INDICATIONS AND DOSAGE1,2

FDA Indication1,2: For the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate® (romiplostim) or Promacta® (eltrombopag) should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk of bleeding. Neither agent should be used in an attempt to normalize platelet counts.

Dosing:
Nplate (romiplostim)1 – Initial dose of 1 mcg/kg once weekly as a subcutaneous injection. Adjust weekly dose by increments of 1 mcg/kg to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelet count is > 400 x 10^9/L. Discontinue romiplostim if platelet count does not increase after 4 weeks at the maximum dose.

Promacta (Eltrombopag)2 - The starting dose of eltrombopag is 50 mg orally once daily for most patients; for patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, the starting dose is 25 mg once daily. Do not exceed a daily dose of 75 mg. Discontinue eltrombopag if the platelet count does not increase after 4 weeks at the maximum dose; also discontinue eltrombopag for important liver test abnormalities or excessive platelet count responses (platelet count >400 x 10^9/L for 2 consecutive weeks at the lowest dose).

CLINICAL RATIONALE
Romiplostim was studied in two 24-week, randomized, double blind, placebo controlled trials for patients with ITP. The protocols for the two studies were identical with the exception of spleen status. The primary endpoint was a durable platelet response which was defined as achieving weekly platelet responses (>50 x 10^9/L) for six or more weeks of the final eight weeks of the study. For patients with a spleen, the durable response rate was 61% in the romiplostim group and 5% in the placebo group (p<0.0001). For patients without a spleen, the durable response rate was 38% in the romiplostim group and 0% in the placebo group (p<0.0013).³
Eltrombopag was studied in ITP in two placebo-controlled studies. In the first study, patients were randomized to receive placebo or eltrombopag 30 mg, 50 mg, or 75 mg once daily for up to six weeks. The primary endpoint was a platelet count of 50,000 per cubic millimeter or more at day 43. Secondary endpoints included bleeding. A platelet count of >50,000 per cubic millimeter was achieved by 81%, 70%, 28%, and 11% of patients in the eltrombopag 75 mg, 50 mg, 30 mg, and placebo groups respectively (p<0.001 for 50 mg and 75 mg compared to placebo). Bleeding events, regardless of grade or cause, occurred in 4%, 7%, 17%, and 14% of patients in the eltrombopag 75 mg, 50 mg, 30 mg, and placebo groups respectively. In the second study, patients were randomized to receive either eltrombopag 50 mg or placebo once daily. The daily dose of eltrombopag could be increased to 75 mg once daily if platelet counts were less than 50,000/mcL on day 22. The primary endpoint was a platelet count of 50,000 per cubic millimeter or more at day 43. Secondary endpoints included bleeding. The primary endpoint was achieved in 58.9% of those in the eltrombopag group and 16.2% in the placebo group (p<0.001). A total of 39% of patients in the eltrombopag group and 69% in the placebo group required a dose increase at day 22. Odds of any bleeding at day 43 were significantly reduced in the eltrombopag group compared to the placebo group (p=0.029).

Administration of both romiplostim and eltrombopag increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Discontinuation of romiplostim and eltrombopag may result in thrombocytopenia of greater severity than was present prior to therapy. This worsened thrombocytopenia may increase the patient’s risk of bleeding, particularly if romiplostim or eltrombopag is discontinued while the patient is on anticoagulants or antiplatelet agents. Eltrombopag has a black boxed warning concerning hepatotoxicity. Serum liver tests (ALT, AST, and bilirubin) should be monitored prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose; eltrombopag should be discontinued if there are progressive or persistent elevations of liver test abnormalities.

In order to measure therapeutic response and monitor safety, patients taking romiplostim or eltrombopag should have routine CBC monitoring, including platelet counts and peripheral blood smears. The CBC should be analyzed before treatment in order to evaluate baseline cellular morphologic abnormalities. The CBC should also be monitored weekly during therapy until the dose and platelet count are stable, and then monthly thereafter. Administered dose of these agents should be adjusted based on measured platelet count. CBC and platelet count should be obtained weekly following discontinuation of these agents; 2 weeks for romiplostim, 4 weeks for eltrombopag.

Prescribers, pharmacies, and patients must enroll in the Nplate NEXUS Program in order to obtain access to romiplostim and the Promacta CARES program to obtain access to eltrombopag. These programs provide educational materials and a mechanism for risk-benefit evaluation. In both programs, prescribers must submit baseline patient data before initiating therapy and will be contacted twice a year by the program in order to verify the provider’s enrolled patient roster and collect safety information. Prescribers are required to report any adverse events that occur. Patients are to receive a medication guide and counseling on the risk and benefits of these drugs.

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

For additional clinical information see the Prime Therapeutics Formulary Chapter 13.1C: Hematopoietic Agents: Colony Stimulating Factors.

REFERENCES

**Document History**

Original Prime Standard criteria approved by P&T UM Committee 02/2009
Initial Client Review Client Specific criteria, approved by HCSC Corporate Clinical Committee 07/2010
ITP (Nplate, Promacta) Prior Authorization

OBJECTIVE
The intent of the prior authorization (PA) requirement for Nplate® and Promacta® is to encourage appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. The PA criteria for Nplate and Promacta direct their use to the single FDA-approved indication for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) in those who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Criteria will limit the approved dose to at or below the maximum FDA-labeled dose and the quantity of Promacta tablets to at or below the quantity limit set by the PA program.

TARGET DRUGS
- Nplate® (romiplostim)
- Promacta® (eltrombopag)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Nplate and Promacta will be approved when ONE of the following are met:

1. The patient has a diagnosis of chronic ITP, and BOTH of the following:
   a. ONE of the following:
      i. The patient has a history of trial and failure of, allergy to, contraindication to, or intolerance of one of the following treatments: a) corticosteroids, b) immunoglobulins OR
      ii. The patient has had an insufficient response to a splenectomy
   b. The requested dose is at or below the FDA-labeled maximum daily dose AND the requested quantity for Promacta is at or below the program quantity limit

2. There is clinical evidence supporting a medically accepted indication for the requested agent for the intended use (e.g., medically accepted indications in compendia [NCCN, AHFS, DrugDex, Clinical Pharmacology] or a published phase 3 clinical trial) or the prescriber has submitted documentation in support of the use of the requested agent for the intended diagnosis or for the prescribed quantity which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months
ITP (Nplate, Promacta) Prior Authorization

ELECTRONIC EDIT
The overall process for a prior authorization will not allow the targeted drugs to adjudicate through the claims system. When a patient requests a targeted drug the system will reject the claim with the message indicating that prior authorization is necessary.

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity per Day Limit*</th>
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<td>Nplate® (romiplostim) subcutaneous injection</td>
<td>82405060002120</td>
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<td>Promacta® (eltrombopag) oral tablet</td>
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* Quantity limit applies to Promacta only

PRIOR AUTHORIZATION CRITERIA QUESTION SET
Nplate (romiplostim) and Promacta (eltrombopag)
Initial and Renewal Evaluation
1. Does the patient have a diagnosis of chronic immune (idiopathic) thrombocytopenic purpura (ITP)?
   If yes, continue to 2. If no, continue to 6.

2. Does the patient have a history of trial and failure of, allergy to, contraindication to, or intolerance of one of the following treatments?
   a. Corticosteroids
   b. Immunoglobulins
   If yes, continue to 5. If no, continue to 3.

3. Has the patient had a splenectomy?
   If yes, continue to 4. If no, continue to 6.

4. Did the patient have an insufficient response to the splenectomy?
   If yes, continue to 5. If no, continue to 6.

5. Is the requested dose at or below the FDA-labeled maximum dose and the requested quantity at or below the program quantity limit?
   If yes, approve for 12 months. If no, continue to 6.

6. Is there clinical evidence supporting a medically accepted indication for the requested agent for the intended use (e.g., medically accepted indications in compendia [NCCN, AHFS, DrugDex, Clinical Pharmacology] or a published phase 3 clinical trial) or has the prescriber submitted and the pharmacist reviewed documentation in support of the requested therapeutic use or prescribed dose for the requested agent in this patient?
   If yes, pharmacist must review and may approve for 12 months based on review of information provided.
   If no, deny.