Cigna covers romiplostim (Nplate®) for the treatment of thrombocytopenia when all of the following criteria are met:

- Diagnosis of chronic immune (idiopathic) thrombocytopenia (ITP)
- Insufficient response to initial therapy with corticosteroids, immunoglobulins, or splenectomy
- Platelet count less than 30,000 mm³ OR platelet count less than 50,000 mm³ and clinical condition increases the risk for bleeding

Initial approval duration is 6 months. Reauthorization for up to 1 year requires all of the following:

- Documentation of beneficial clinical response as evidenced by increased platelet counts
- Clinical condition increases the risk for bleeding

Cigna does not cover the use of romiplostim (Nplate®) for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- Treatment of thrombocytopenia due to myelodysplastic syndrome (MDS)
- Normalization of platelet counts

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to romiplostim (Nplate) therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage
**FDA Approved Indications**

Nplate is indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP) 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 chronic ITP.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts.

**FDA Recommended Dosing**

Use the lowest dose of Nplate to achieve and maintain a platelet count ≥ 50 x 10⁹/L as necessary to reduce the risk for bleeding. Administer Nplate as a weekly subcutaneous injection with dose adjustments based upon the platelet count response.

The prescribed Nplate dose may consist of a very small volume (e.g., 0.15 mL). Administer Nplate only with a syringe that contains 0.01 mL graduations.

**Initial Dose:**
The initial dose for Nplate is 1 mcg/kg based on actual body weight.

**Dose Adjustments:**
Use the actual body weight at initiation of therapy, then adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 x 10⁹/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. In clinical studies, most patients who responded to Nplate achieved and maintained platelet counts ≥ 50 x 10⁹/L with a median dose of 2 mcg/kg.

During Nplate therapy, assess CBCs, including platelet counts, weekly until a stable platelet count (≥ 50 x 10⁹/L for at least 4 weeks without dose adjustment) has been achieved. Obtain CBCs, including platelet counts, monthly thereafter.

Adjust the dose as follows:
- If the platelet count is < 50 x 10⁹/L, increase the dose by 1 mcg/kg.
- If the platelet count is > 200 x 10⁹/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If the platelet count is > 400 x 10⁹/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 x 10⁹/L, resume Nplate at a dose reduced by 1 mcg/kg.

**Discontinuation:**
Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of Nplate therapy at the maximum weekly dose of 10 mcg/kg. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate.

**Drug Availability**

Nplate is supplied in single-dose vials containing 250 mcg and 500 mcg of romiplostim. In December 2011, the FDA approved modification to the Risk Evaluation and Mitigation Strategies (REMS) for romiplostim which removed the requirements for restricted distribution and additional safety data collection that had been in place. REMS for romiplostim is still required and includes a communication plan to inform healthcare professionals about the changes to the REMS program, as well as the serious risks associated with treatment.

**General Background**

**Pharmacology**
Romiplostim is a recombinant fusion protein that binds thrombopoietin and subsequently stimulates platelet production.
Guidelines
American Society of Hematology (ASH)
The American Society of Hematology uses terminology from an International Working Group (IWG), which is a panel of experts in adult and pediatric immune thrombocytopenia (ITP). While they note these definitions have not been validated, the authors of the ASH guidelines state they incorporated the IWG terminology whenever possible. The IWG defines newly diagnosed ITP as from the time of diagnosis to 3 months, persistent ITP as 3-12 months from diagnosis, and chronic ITP as greater than 12 months from diagnosis. (Neunert, 2011)

For newly diagnosed adult ITP, ASH recommends treatment if the platelet count is less than 30 X 10^9/L. The preferred treatment is longer courses of corticosteroids over shorter courses of corticosteroids or IVIG. IVIG is recommended in combination with corticosteroids if there is a need for a rapid increase in platelet count and is recommended first-line if corticosteroids are contraindicated. For patients who fail initial corticosteroid therapy, splenectomy is recommended. Thrombopoietin receptor agonists (e.g., eltrombopag, romiplostim) are recommended if splenectomy fails or for those who are not candidates for splenectomy and failed at least one other treatment option and can be considered prior to splenectomy if failed another therapy such as corticosteroids or IVIG. Another treatment option for those at risk for bleeding who fail corticosteroids, IVIG, or splenectomy is rituximab. (Neunert, 2011)

For newly diagnosed pediatric ITP, ASH recommends observation only regardless of the platelet count if there is no bleeding or mild bleeding, such as skin manifestations only. If treatment is needed, IVIG is considered a first line agent or a short course of corticosteroids. Rituximab or high-dose dexamethasone can be considered in pediatric patients with continued ITP symptoms (i.e., significant ongoing bleeding) despite treatment with IVIG, conventional-dose corticosteroids, or anti-D. Rituximab or high-dose dexamethasone are also options to avoid splenectomy or if splenectomy fails. (Neunert, 2011)

For ITP associated with human immunodeficiency virus (HIV) or hepatitis C, ASH recommends treating the underlying virus. If treatment is needed, IVIG is the recommended initial option for hepatitis C-associated ITP and one of the options for HIV-associated ITP. For ITP in pregnancy, IVIG or corticosteroids should be given. (Neunert, 2011)

Clinical Efficacy
• FDA Approved Indication
The safety and efficacy of romiplostim were assessed in two parallel trials evaluating romiplostim in 63 splenectomized and 62 non-splenectomized patients with chronic ITP who had at least one prior treatment and a platelet count less than or equal to 30 x10^9/L. Compared to placebo, romiplostim increases and maintains platelet counts in ITP patients after 6 months of treatment. Durable platelet response, defined as a platelet count greater than or equal to 50,000/µL for any 6 of the last 8 weeks of treatment, for the patients treated with romiplostim was 41/83 (49%) compared to placebo at 1/42 (2%). Overall response to romiplostim was lower in splenectomized patients than non-splenectomized patients, but both groups were superior to placebo (p<0.05 for each). (Kuter, 2008)

An open-label study tested utility of romiplostim as a means of delaying or avoiding a splenectomy. Two hundred and thirty-four (234) non-splenectomized individuals were randomly assigned to receive romiplostim or standard of care for 52 weeks. Patients receiving romiplostim had a significantly lower incidence of treatment failure (11% vs. 30%, p<0.001) and splenectomy (9% vs. 36%, p<0.001) than those receiving the standard of care. Patients treated with romiplostim also had a lower rate of bleeding events, fewer blood transfusions, and greater improvement in the quality of life than the standard of care group. (Kuter, 2010) Another publication describes up to 5 years of weekly treatment with romiplostim in 292 adult ITP patients in a long-term, single arm, open-label study concluding that romiplostim was safe and well tolerated in over 614 patient-years of exposure in ITP patients, and that efficacy was maintained with stable dosing for up to 5 years of continuous treatment, while providing steady platelet counts, low rates of bleeding, and low needs for concurrent medications and rescue treatments for ITP. (Kuter, 2013)

Randomized controlled trials comparing thrombopoietin (TPO) receptor agonists alone, or in combination with other drugs, to placebo, no treatment, other drugs, splenectomy or another TPO receptor agonist were evaluated to determine the efficacy and safety of TPO receptors in patients with chronic ITP in a Cochrane Systematic Review/Meta-analysis. Six trials with 808 patients were included. Five studies compared TPO receptor agonists with placebo (romiplostim: 100, eltrombopag, 299, placebo: 175); one study compared TPO receptor agonists with standard of care (SOC) (romiplostim: 157; SOC: 77) where SOC included a variety of therapies, such as...
glucocorticoid, anti-D immune globulin, IVIg, rituximab, azathioprine, etc. Overall survival, one of the primary outcomes, was not studied by these RCTs and the authors could not estimate number needed to treat (NNT). Another primary outcome, improving significant bleeding events, did not reveal any significant differences between the TPO receptor agonists groups and the control group (placebo or SOC) (versus placebo risk ration (RR) 0.48, 95% confidence interval (CI) 0.20 to 1.15; versus SOC RR 0.49, 95% CI 0.15 to 1.63). The authors concluded overall that there was currently no evidence to support that TPO receptor agonists are effective in chronic ITP. Compared to placebo or SOC, despite significantly increased platelet response, there was no evidence to demonstrate that TPO receptor agonists did improve significant bleeding events in chronic ITP. The effect on overall survival awaits further analysis. Although long-term studies are lacking, current data demonstrated adverse effects of TPO receptor agonists were similar to that of placebo and SOC. More research is needed to explore the role of TPO receptor agonists in the treatment of chronic ITP more fully. (Zeng, 2011)

In the absence of head-to-head randomized controlled trials, an evaluation was performed using a Bayesian meta-regression model to indirectly compare effectiveness of the thrombopoietin mimetics romiplostim and eltrombopag for increasing platelet counts, and contrasted the results with those of non-Bayesian approaches. Placebo-controlled trials of 24 weeks duration (two romiplostim and one eltrombopag) were included. The indirect evidence suggests romiplostim significantly improves overall platelet response compared with eltrombopag. Bayesian meta-regression gave an odds ratio (OR) for eltrombopag versus romiplostim of 0.11 (95% credible interval 0.02-0.66); p values and Bayesian posterior probabilities ranged from 0.01 to 0.05 for all analyses. There was no significant difference in durable platelet response in any of the analyses, although the direction of effect favored romiplostim (OR = 0.15; 95% credible interval, 0.01-1.88); p values and Bayesian posterior probabilities ranged from 0.08 to 0.40 across analyses. Results were consistent between analyses. (Cooper, 2012)

Experimental, Investigational, or Unproven Uses
Romiplostim is being investigated for use in other types of thrombocytopenic conditions, including myelodysplastic syndrome (MDS); hepatitis/HIV associated; post hematopoietic stem cell transplantation; cancer/chemotherapy induced/related; Evans syndrome, graft versus host disease (GVHD); chronic liver disease prior to biopsy to reduce morbidity and mortality; and as a stem cell mobilizer in transplant. At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of romiplostim for these indications. The use of romiplostim in the management of pediatric ITP continues to be investigated; however, its place in therapy has not been established.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>J2796</td>
<td>Injection, romiplostim, 10 micrograms</td>
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References