Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

Plan: Aetna Better Health

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Type of Submission – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy **must** be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0768 Romiplostim (Nplate)**

This CPB is revised to state that the initiation of romiplostim (Nplate) for chronic or persistent primary immune thrombocytopenic purpura (ITP) is considered medically necessary when both of the following criteria are met: 1) member has had an inadequate response or intolerance to prior therapy with corticosteroids, immunoglobulins, or splenectomy; and 2) member has an untransfused platelet count of less than 30 x 10^9/L, or 30 x 10^9/L to 50 x 10^9/L with symptomatic bleeding or risk factors for bleeding. This CPB is revised to state that continued use of romiplostim for chronic ITP is considered medically necessary when any of the following criteria are met: 1) member has a current platelet count of less than 50 x 10^9/L; 2) member has a platelet count of 50 x 10^9/L to 200 x 10^9/L; or 3) member has a platelet count of greater than 200 x 10^9/L and less than 400 x 10^9/L for whom romiplostim dosing will be adjusted to achieve platelet count sufficient to avoid clinically important bleeding. This CPB is revised to state that romiplostim for myelodysplastic syndrome is considered medically necessary when both of the following criteria are met: 1) member has lower risk disease defined as Revised International Prognostic Scoring System (IPSS-R) (Very Low, Low, Intermediate), International Prognostic Scoring System (IPSS) (Low/Intermediate-1), or WHO classification-based Prognostic Scoring System (WPSS) (Very Low, Low, Intermediate); and 2) member has severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents such as azacitidine and decitabine or immunosuppressive therapy. This CPB is revised to state that continued use of romiplostim for MDS is considered medically necessary for members who receive benefit from therapy (e.g., increased platelet counts, decreased bleeding events, reduced need for platelet transfusions). This CPB is revised to state that concomitant use of romiplostim with spleen tyrosine kinase inhibitors (e.g., Tavalisse) is considered experimental and investigational because of the lack of evidence of safety and effectiveness of these combinations.
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<th>Name of Authorized Individual (Please type or print):</th>
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<td>Dr. Bernard Lewin, M.D.</td>
<td>Bernard Lewin, M.D.</td>
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Revised July 22, 2019
Romiplostim (Nplate)

Aetna considers romiplostim (Nplate) medically necessary for the following indications:

**I. Chronic or Persistent Primary Immune (Idiopathic) Thrombocytopenic Purpura (ITP)**

Aetna considers the initiation of romiplostim (Nplate) medically necessary for the treatment of chronic or persistent ITP when both of the following criteria are met:

A. Member has had an inadequate response or intolerance to prior therapy with corticosteroids, immunoglobulins, or splenectomy; and

B. Member has untransfused platelet count of less than 30 x 10^9/L, or 30 x 10^9/L to 50 x 10^9/L with symptomatic bleeding or risk factors for bleeding (see appendix).

**II. Continuation Criteria for Use in Chronic ITP**

Aetna considers continued (maintenance) use of romiplostim medically necessary in chronic ITP when any of the following criteria are met:
A. Member has a current platelet count less than $50 \times 10^9$/L for whom the platelet count is not sufficient to prevent clinically important bleeding and who have not received maximal dose of romiplostim for at least 4 weeks (authorization for 3 months); or
B. Member has a current platelet count less than $50 \times 10^9$/L for whom platelet count is sufficient to prevent clinically important bleeding; or
C. Member has a platelet count of $50 \times 10^9$/L to $200 \times 10^9$/L; or
D. Member has a platelet count greater than $200 \times 10^9$/L and less than $400 \times 10^9$/L for whom romiplostim dosing will be adjusted to achieve platelet count sufficient to avoid clinically important bleeding.

Note: Romiplostim should not be utilized to normalize platelet counts

III. Myelodysplastic Syndromes (MDS)

Aetna considers romiplostim medically necessary for treatment myelodysplastic syndromes when both of the following criteria are met

A. Member has lower risk disease defined as Revised International Prognostic Scoring System (IPSS-R) (Very Low, Low, Intermediate), International Prognostic Scoring System (IPSS) (Low/Intermediate-1), or WHO classification-based Prognostic Scoring System (WPSS) (Very Low, Low, Intermediate); and
B. Member has severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents such as azacitidine and decitabine or immunosuppressive therapy.

IV. Continuation criteria for use in myelodysplastic syndromes (MDS)

Aetna considers continued use of romiplostim medically necessary in MDS for members who receive benefit from therapy (e.g., increased platelet counts, decreased bleeding events, reduced need for platelet transfusions.

V. Concomitant use of romiplostim with other thrombopoetin receptor agonists (e.g., eltrombopag (Promacta), avatrombopag (Doptelet) or lusutrombopag (Mulpleta) or spleen tyrosine kinase inhibitors (e.g., Tavalisse) is considered experimental and investigational because of the lack of evidence of safety and effectiveness of these combinations.
VI. Romiplostim is considered not medically necessary in the following:

A. persons with ITP and previous documented failure of romiplostim; or
B. persons with loss of response to romiplostim after four weeks at maximum dose.

Note: Persons who have lost response to romiplostim should be assessed for other possible etiologies (e.g., antibodies to romiplostim and bone marrow fibrosis) and romiplostim discontinued.

VII. Experimental and Investigational

Aetna considers romiplostim experimental and investigational for the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

A. Stem cell mobilization
B. Thrombocytopenia due to chemotherapy and/or radiation therapy
C. Thrombocytopenia during pregnancy
D. Thrombocytopenia following allogeneic stem cell transplantation
E. Evans syndrome
F. Graft-versus-host disease
G. Hepatitis-C.

Background

Nplate (romiplostim) is a thrombopoiesis stimulating peptibody developed to stimulate platelet production. It binds to and stimulates the thrombopoietin (TPO) receptor. It has no sequence homology with endogenous TPO, and therefore is not expected to elicit cross-reacting antibodies that cause thrombocytopenia, a problem that has occurred with previously studied recombinant TPO agents.

Romiplostim (Nplate™, Amgen, Inc., Thousand Oaks, CA) was approved by the Food and Drug Administration (FDA) on August 22, 2008 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. The FDA-approved labeling states that romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding and that it should not be used to normalize platelet counts.

The safety and efficacy of romiplostim were assessed in 2 double-blind, placebo-controlled clinical studies of 125 adult patients with chronic ITP and in an open-label extension study. In these studies, treatment with romiplostim resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg of romiplostim, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above 50 x 10^9/L for 7 out of 8 patients with chronic ITP who received 6 weekly doses of romiplostim at 1 mcg/kg.

Kuter et al (2008) assessed the long-term effects of romiplostim in splenectomized and non-splenectomized patients with ITP in 2 parallel trials. A total of 63 splenectomized and 62 non-splenectomized patients with ITP with a mean of 3 platelet counts of 30 x 10^9/L or less were randomly assigned 2:1 to subcutaneous injections of romiplostim (n = 42 in the splenectomized study and n = 41 in the non-splenectomized study) or placebo (n = 21 in both studies) every week for 24 weeks. Doses of romiplostim were adjusted to maintain platelet counts of 50 x 10^9/L to 200 x 10^9/L. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count greater than or equal to 50 x 10^9/L during 6 or more of the last 8 weeks of treatment) and treatment safety. The authors reported that a durable platelet response was achieved by 38 % (16/42) of the splenectomized patients given romiplostim versus none (0/21) of the placebo patients, and by 61 % (25/41) of the non-splenectomized patients given romiplostim versus 0.05 % (1/21) given placebo. Eighty-seven percent (20/23) of patients given romiplostim (12/12 splenectomized and 72 % (8/11) non-splenectomized patients) reduced or discontinued concurrent therapy compared with 38 % (6/16) of those given placebo (1/6 splenectomized and 5/10 non-splenectomized patients). Adverse events were reported to be similar in both groups. Furthermore, no antibodies against romiplostim or thrombopoietin were detected. The authors concluded that romiplostim was well-tolerated and increased and maintained platelet counts in splenectomized and non-splenectomized patients with ITP and that many patients were able to reduce or discontinue other ITP medications.
Following completion of the placebo-controlled studies, 100 patients entered an extension study of long-term romiplostim therapy. The majority of patients maintained platelet counts of 50,000/mcL or greater throughout the study with a median duration of romiplostim treatment of 60 weeks and a maximum duration of 96 weeks.

The major safety concerns consisted of risks for bone marrow reticulin formation and worsened thrombocytopenia (compared to baseline) following romiplostim discontinuation. Other potential risks include marrow fibrosis during long-term therapy or thromboses due to excessive platelet increases.

Vadhan-Raj (2009) stated that despite the extensive efforts in the clinical development of thrombopoietic agents in the past decade, recombinant interleukin-11 (IL-11) is the only agent currently approved by the FDA for thrombocytopenia induced by chemotherapy. The use of this agent is limited due to its narrow therapeutic index. While promising biologic activity was observed with recombinant thrombopoietins (TPOs) in non-myeloablative clinical settings, further clinical development was halted due to evidence of neutralizing antibodies to pegylated recombinant human megakaryocyte growth and development factor. Recently, a number of novel TPO receptor agonists have been developed with promising clinical activity and a lesser potential for immunogenicity. Several of these second-generation platelet-stimulating agents are currently in clinical development, including peptide (romiplostim) and non-peptide (eltrombopag and AKR501) mimetics. The clinical trials of romiplostim and eltrombopag are currently ongoing to optimize their dose and schedule in ameliorating chemotherapy-induced thrombocytopenia.

Kuter (2011) noted that thrombocytopenia is a common clinical problem associated with a wide range of medical conditions including ITP, chemotherapy-induced thrombocytopenia (CIT), hepatitis C-related thrombocytopenia, and MDS. Until recently, the only treatments for thrombocytopenia were to alleviate the underlying cause or to provide platelet transfusions. With the discovery and recent clinical availability of TPO mimetics, a new treatment option has emerged. Two TPO mimetics are currently clinically available for treating ITP: romiplostim (an injectable peptide TPO mimetic) and eltrombopag (a non-peptide, orally available TPO mimetic). The author reviewed the development, biology, and clinical trials with romiplostim. With few adverse effects, romiplostim is effective in raising the platelet count in over 80% of ITP patients, allowing them to discontinue other therapies,
reduce the need for splenectomy, and improve their quality of life. Long-term theoretical side effects of romiplostim treatment include reticulin formation, thrombo-embolism, and antibody formation to romiplostim. A practical way of using romiplostim is provided: a higher starting dose of 3 mg/kg is recommended along with efforts to avoid withholding the dose. The author concluded that future studies are needed to evaluate the utility of romiplostim in CIT, hepatitis-C related thrombocytopenia, and MDS.

In a review on "Novel agents and approaches for stem cell mobilization in normal donors and patients", Bakanay and Demirer (2012) listed thrombopoietin-receptor agonists including romiplostim as one of the investigational agents. They noted that in the future, thrombopoietin-receptor agonists may be potential adjuncts to granulocyte colony-stimulating factor in poor mobilizers.

Evans syndrome is an autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia and immune thrombocytopenia. It may be primary (idiopathic), or associated with other diseases. First-line therapy is immunosuppression; and 2nd-line therapy includes danazol and splenectomy. Gonzalez-Nieto et al (2011) reported a case of a man diagnosed with systemic lupus erythematosus, associated anti-phospholipid syndrome and Evans syndrome, who developed a severe thrombocytopenia refractory to treatment with first-line drugs, cyclophosphamide and rituximab, and who responded to romiplostim with a normalization of the platelet recount, which later enabled a therapeutic splenectomy to be performed. Moreover, UpToDate reviews on "Treatment of autoimmune hemolytic anemia: Warm agglutinins" (Rosse and Schrier, 2012) and "Autoimmune hemolytic anemia in children" (Ware, 2012) do not mention the use of romiplostim as a therapeutic option.

Ruiz-Delgado et al (2011) stated that thrombocytopenia ensuing during acute graft-versus-host disease (GVHD) is multi-factorial and may significantly compromise the prognosis of the patient; non-immune persistent thrombocytopenia has been considered as an adverse prognostic factor in GVHD. These investigators described the case of a 10-year old girl who developed steroid-refractory thrombocytopenia and who responded promptly to the subcutaneous delivery of romiplostin. The authors noted that to the best of their knowledge, this is the first description of the usefulness of the peptibody in the setting of GVHD. However, UpToDate reviews on "Overview of immunosuppressive agents used for
prevention and treatment of graft-versus-host disease” (Chao, 2012a), “Treatment of chronic graft-versus-host disease” (Chao, 2012b), and “Treatment of acute graft-versus-host disease: Clinical trials” (Chao, 2012c) do not mention the use of romiplostim as a therapeutic option.

Buccoliero et al (2014) described a case of a 64-year old man with a history of ITP which had required several treatments including splenectomy, and with chronic hepatitis C virus (HCV) infection untreated due to severe thrombocytopenia. In March 2011, platelet count was 14,000/mmC and a thrombopoietic therapy with romiplostim was initiated at the dose of 2 ug/kg/week that was increased to 8 ug/kg/week. At week 32, platelet count was 65,000/mmC and an anti-HCV therapy with peginterferon and ribavirin was then started. At baseline laboratory tests indicated AST 99 IU/l, ALT 125 IU/l, HCV_RNA 3,220 UI/ml and HCV genotype 2a/2c. An early virological response (EVR) with normalization of transaminases in the course of anti-viral therapy, such as a sustained virological response (SVR) after its interruption were recorded. Therefore, a satisfactory platelet count (range of 54,000 to 179,000/mmC) at the dose of 4 ug/week during anti-viral therapy, such as at the dose of 2 ug/kg/week after anti-viral interruption (range 65,000 to 292,000/mmC) was recorded. Romiplostim proved safe and effective in the course of anti-viral treatment. Therefore, it permitted the start of anti-HCV therapy despite severe thrombocytopenia and also avoided any peg-interferon dosage modification or discontinuation. The authors stated that further prospective studies in larger patient cohort should be encouraged to validate this strategy.

Parameswaran et al (2014) reported on a series of 20 patients who had protracted CIT and were treated with romiplostim. These researchers performed a retrospective review of the use of romiplostim for dose-limiting CIT at Memorial Sloan-Kettering Cancer Center from 2010 to 2012. Romiplostim was initiated at 1 to 2 ug/kg weekly, with dose escalation by 1 ug/kg per week until recovery of platelets (greater than or equal to 100 × 10(9)/L). If patients resumed chemotherapy, weekly romiplostim was continued. Romiplostim improved platelet counts in all 20 patients. In 19 of 20 patients, platelet counts of greater than or equal to 100 × 10 (9)/L were achieved. The mean dose of romiplostim to achieve adequate platelet recovery was 2.9 ug/kg (range of 1.0 to 5.1); 16 patients achieved platelet recovery by 2 weeks. Fifteen patients resumed cytotoxic chemotherapy with continued romiplostim support and 14 tolerated at least 2 subsequent cycles of chemotherapy, on schedule, without recurrence of dose-limiting CIT. Sepsis prevented continued chemotherapy in 1 patient. No resistance to romiplostim was
observed. Three deep vein thromboses (DVT) were observed; 1 of which was a recurrent DVT in a patient who had previously experienced a DVT and was off anti-coagulation. Three DVTs within 20 patients is within the anticipated thrombosis rates of patients with active cancer on chemotherapy. The authors concluded that romiplostim resulted in improvement in platelet counts, allowing resumption of chemotherapy without recurrence of dose-limiting CIT. No treatment-related toxicity was observed, but this would need to be confirmed in a larger, prospective trial. They stated that their series differed from prior studies in that they selected only those patients who had already demonstrated persistent thrombocytopenia, and they continued weekly romiplostim during chemotherapy. Romiplostim may be a safe and effective treatment for CIT.

Yamada and associates (2014) reported on the case of a woman in her 60s who was referred to the authors' department with advanced rectal cancer and multiple unresectable metastases of the liver and peritoneum. She had been diagnosed with ITP in her 20s, with a platelet count maintained at approximately 1.0×10(4)/μL by prednisolone; on admission, her platelet count was 0.9×10(4)/μL. Romiplostim was administered prior to chemotherapy. Her platelet count increased to about 10.0×10(4)/μL during chemotherapy with oxaliplatin plus capecitabine, and she developed DVT requiring inferior vena cava filter placement and anti-coagulation. No other severe adverse events occurred. The authors noted that there is no standard regimen for the treatment of solid tumors in patients with ITP. This was the first reported case of the concomitant use of romiplostim and chemotherapy for advanced rectal cancer.

Myelodysplastic Syndromes (MDS)

According to the FDA (2008), in a single-arm trial investigating the use of romiplostim in myelodysplastic syndromes (MDS), 11 of 44 patients were reported as having possible disease progression, among whom 4 patients developed acute myelogenous leukemia. Randomized, controlled studies are needed to determine the risks and benefits of romiplostim in these patients. In the controlled studies of patients with chronic ITP, the incidence of hematologic malignancies was low and similar between romiplostim and placebo. Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
Kantarjian and colleagues (2010) evaluated the safety and effectiveness of romiplostim for treatment of thrombocytopenic patients with MDS. Eligible patients had lower-risk MDS (International Prognostic Scoring System low or intermediate 1), a mean baseline platelet count less than or equal to 50 x 10⁹/L, and were only receiving supportive care. Patients received 3 injections of 300, 700, 1,000, or 1,500 microg romiplostim at weekly intervals. After evaluation of platelet response at week 4, patients could continue to receive romiplostim in a treatment extension phase for up to 1 year. All 44 patients who enrolled completed the treatment phase; 41 patients continued into the extension phase. Median platelet counts increased throughout the study, from fewer than 30 x 10⁹/L at baseline to 60, 73, 38, and 58 x 10⁹/L at week 4 for the 300-, 700-, 1,000-, and 1,500 -microg dose cohorts, respectively. A durable platelet response (per International Working Group 2000 criteria for 8 consecutive weeks independent of platelet transfusions) was achieved by 19 patients (46%). The incidence of bleeding events and platelet transfusions was less common among patients who achieved a durable platelet response than those who did not (4.3 versus 39.3 per 100 patient-weeks). Forty-three patients (98%) reported 1 or more adverse events. Treatment-related serious adverse events were reported in 5 patients (11%), all of whom were in the 1,500-microg dose cohort. Two patients progressed to acute myeloid leukemia during the study. No neutralizing antibodies to either romiplostim or endogenous thrombopoietin were seen. The authors concluded that romiplostim appeared well-tolerated in this study and may be a useful treatment for patients with MDS and thrombocytopenia. The key drawback of this study was the lack of a control group. These investigators stated that ongoing randomized controlled trials and future combination studies will optimize the dose schedules of romiplostim and define its precise therapeutic role in MDS.

In a phase II, multi-center, open-label study, Sekeres et al (2011) examined the effects of subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with lower risk MDS. A total of 28 thrombocytopenic patients with lower risk MDS were assigned to receive romiplostim 750 μg administered subcutaneously either weekly or bi-weekly or administered as bi-weekly intravenous injections for 8 weeks. Patients also could enter a 1-year study extension phase. At least 1 adverse event was observed in 93% of patients. The most common adverse events were fatigue and headache (18% for both, and 5 events were grade 3 or 4. There was 1 serious treatment-related adverse event in the bi-weekly intravenous cohort (hypersensitivity). This hypersensitivity resolved without discontinuation of study treatment. No patients developed neutralizing
antibodies or bone marrow fibrosis. Of the patients who completed 8 weeks of
treatment, 57 % had a complete platelet response, an additional 8 % had a major
platelet response, and 61 % did not require a platelet transfusion during this
period. Weekly subcutaneous injections achieved the highest mean trough
concentrations. The authors concluded that the safety and efficacy profiles of
romiplostim in this study suggested that weekly subcutaneous administration of 750
μg romiplostim is an appropriate starting dose for future clinical studies in patients
with MDS and thrombocytopenia.

Prica et al (2014) stated that thrombocytopenia is common (40 to 65 %) and
potentially serious in MDS. These investigators performed a systematic review to
determine the safety and effectiveness of adding a thrombopoietin-receptor
(THPO-R) agonist to standard MDS treatment. MEDLINE, EMBASE and CENTRAL
databases were searched. These researchers included randomized controlled trials
(RCTs) comparing a THPO-R agonist to placebo. A meta-analysis of the effects
was performed. End-points included bleeding and platelet transfusion rates, risk of
progression to AML and mortality. A total of 384 patients from 5 trials were
included, 4 using romiplostim and 1 using eltrombopag. Overall, the relative risk
(RR) of bleeding with romiplostim versus placebo was 0.84 [95 % CI: 0.57 to 1.24].
However, compared to placebo, romiplostim significantly decreased the exposure-
adjusted bleeding rate (RR 0.92; 95 % CI: 0.86 to 0.99), as well as the exposure-
adjusted platelet transfusion rate (RR 0.69; 95 % CI: 0.53 to 0.88). The RR of AML
progression with romiplostim was 1.36 (95 % CI: 0.54 to 3·40), however the
outcome data were judged as higher risk of bias. The authors concluded that
romiplostim is promising in its ability to decrease patient-important outcomes:
bleeding and platelet transfusion need. Moreover, they stated that although the risk
of AML progression was not increased, due to unclear risk of bias in the data, this
safety concern is difficult to assess. These investigators stated that romiplostim
cannot yet be routinely recommended.

Giagounidis and colleagues (2014) evaluated the effectiveness of romiplostim in
patients who had thrombocytopenia with low-risk/intermediate-1-risk MDS. Patients
who had thrombocytopenia with low-risk/intermediate-1-risk MDS (n = 250) were
randomized 2:1 to receive romiplostim or placebo weekly for 58 weeks. The
primary end-point was the number of clinically significant bleeding events (CSBEs)
per patient-had a hazard ratio for romiplostim : placebo of 0.83 (95 % confidence
interval [CI], 0.66 to 1.05; p = 0.13). Clinically significant bleeding events were
reduced significantly in the romiplostim group for patients who had baseline platelet
counts greater than or equal to 20 × 10(9) /L (p < 0.0001). For patients who had baseline platelet counts less than 20 × 10(9) /L, there was no difference in the number of CSBEs, but the platelet transfusion rates were higher in the placebo group (p < 0.0001), which may have affected the overall CSBE results in this group with severe thrombocytopenia. The incidence of bleeding events was reduced significantly in the romiplostim group (relative risk, 0.92), as were protocol-defined platelet transfusions (relative risk, 0.77). Platelet response rates according to 2006 International Working Group criteria were higher for the group that received romiplostim (odds ratio, 15.6). On the basis of interim data, an independent data monitoring committee advised halting study drug because of concerns regarding excess blasts and AML rates with romiplostim (interim hazard ratio, 2.51). At 58 weeks, the acute myeloid leukemia (AML) rates were 6 % in the romiplostim group and 4.9 % in the placebo group (hazard ratio, 1.20; 95 % CI: 0.38 to 3.84), and the overall survival (OS) rates were similar. The authors concluded that romiplostim treatment in patients with low-risk/intermediate-1-risk MDS increased platelet counts and decreased the number of bleeding events and platelet transfusions. Although study drug was discontinued because of an initial concern of AML risk, survival and AML rates were similar with romiplostim and placebo.

Kantarjian et al. (2018) conducted a 5-year follow-up study to evaluate the long-term risk of leukemic progression in thrombocytopenic patients with lower-risk MDS treated with romiplostim or placebo in the published (Gigounidis et al, 2014) phase 2, multicenter, double-blind trial, which included 250 patients and resulted in early discontinuation of romiplostim due to potential for disease progression to AML. The primary outcomes for this long-term follow-up were survival and progression to AML. Progression to AML was defined as either 20% blasts or more after 4 weeks from romiplostim discontinuation. Out of the 250 patients, 210 (84%) entered the 5-year long-term follow-up. At the end of follow-up, proportions of patients with AML (12% in the romiplostim group vs 11% in the placebo group (p=0.88)) and proportions who died (p=0.89) were not significantly different between the two groups. The authors concluded that their results indicate that use of romiplostim is probably not associated with any increased risk of AML or death, despite initial concerns.

Nplate (romiplostim) is not FDA-approved for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP (Amgen, 2018).
The prognosis and treatment for MDS vary depending on a person's International Prognostic Scoring System (IPSS) score. Those with a low/intermediate-1 risk score may live with their disease for a number of years. People with higher scores (e.g., intermediate-2 and high risk; IPSS ≥ 1.5) are at higher risk of transformation to acute myelogenous leukemia. Most people with high-risk disease die from their disease within 1 year of diagnosis (Advani, 2006).

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (2019) lists myelodysplastic syndromes as a recommended indication of romiplostim for the treatment of lower risk disease in patients with severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents, immunosuppressive therapy, or clinical trial. Lower risk is defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate). The NCCN guidelines on "Myelodysplastic syndromes" (version 2.2019) state that "in a randomized study including patients low- or int-1-risk MDS (n=250), romiplostim was associated with increased platelet counts and decreased overall bleeding events (p=0.26 after 58 weeks of treatment compared to the placebo group). However, due to the early drug discontinuation, interpretation of these data is limited." The study drug, romiplostim, was discontinued early because of the potential risk for disease progression to AML.

NCCN notes that an open-label extension study evaluated the long-term efficacy and safety of romiplostim in 60 patients with lower-risk MDS and found that most achieved durable responses. "A model to predict response to romiplostim indicated that lower-risk MDS, lower baseline TPO levels (less than 500 pg/mL), and limited platelet transfusion history, had the greatest effect on subsequent platelet response to romiplostim". NCCN does point out that romiplostim is not currently approved for use in persons with MDS.

A review in UpToDate on "Management of the complications of the myelodysplastic syndromes" (Estey and Schrier, 2019) discussed the clinical trial by Giagounidis et al. (2014) that included 250 patients with thrombocytopenia with low-risk/intermediate 1-risk MDS who were randomized 2:1 to receive romiplostim or placebo weekly for 58 weeks. Esty and Schrier state that romiplostim should not be used routinely in MDS based on this clinical trial; however, it appears reasonable to consider use in patients with bleeding due to low platelet counts who do not respond to transfusions and in whom aminocaproic acid has been unsuccessful.
Pediatric Use

Nplate (romiplostim) is FDA-approved in pediatric patients 1 year of age and older with ITP for at least 6 months and who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy (Amgen, 2018).

Berrueco and colleagues (2018) stated that until a few years ago, splenectomy was one of the main strategies for treatment of immune thrombocytopenia (ITP) in adults and children aged more than 5 years. After the introduction of rituximab, pharmacological treatment started to displace surgery as a 2nd-line treatment. At present, many experts recommend the use of receptor agonists (TPO-Ras; eltrombopag and romiplostim) in patients that do not respond to initial treatment with corticosteroids and immunoglobulin before the use of rituximab and surgery. However, studies that compare both therapeutic options have yet to be conducted. In general, and while most guidelines do not recommend splenectomy until ITP has lasted a minimum of 12 months, its use remains controversial. Some patients, as those aged less than 5 years are not eligible for surgery, in other cases parents or legal guardians refuse splenectomy. Finally, sometimes the primary goal of treatment is to improve the quality of life (cases where medical treatment would a priori be preferred over surgical treatment). In all other patients, those who are actually candidates for splenectomy, the risks associated with this irreversible procedure. Thus, despite a good initial response (70 to 85 % of cases) and the fact that most patients maintain a normal platelet count 5 years post-intervention (60 to 70 % of cases), one cannot ignore the associated morbidity: the risk of infection in splenectomized patients is as high as 11 to 16 % even with correct vaccination and administration of antibiotic prophylaxis, the proportion of patients that develop thrombosis after surgery ranges between 1.6 and 4.3 %, and the risk of severe intra-operative or post-operative hemorrhage is of 0.78 %. Thus, since the benefits of splenectomy do not seem to outweigh its disadvantages in children, this intervention should only be used in selected cases: patients who cannot tolerate or do not respond to medical treatment, including corticosteroids, immunoglobulins, TPO-RAs and even immunosuppressive therapy. Splenectomy is also clearly indicated in patients with life-threatening hemorrhage, although this is an extremely rare event. Lastly, splenectomy can also be considered in patients that have a poor health-related quality of life despite receiving other treatment, or at the request of the family. The authors stated that the latest recommendations call for exhausting all options of medical treatment in children with chronic ITP before resorting to splenectomy, with especial emphasis on the use of TPO-Ras.
Grace and associates (2019) noted that while many children with ITP can be safely observed, treatments are often needed for various reasons, including to decrease bleeding, or to improve health related quality of life (HRQoL). There are a number of available 2nd-line treatments, including rituximab, thrombopoietin-receptor agonists, oral immunosuppressive agents, and splenectomy, but data comparing treatment outcomes are lacking. ICON1 is a prospective, multi-center, observational study of 120 children starting 2nd-line treatments for ITP designed to compare treatment outcomes including platelet count, bleeding, and HRQoL utilizing the Kids ITP Tool (KIT). While all treatments resulted in increased platelet counts, romiplostim had the most pronounced effect at 6 months (p = 0.04). Only patients on romiplostim and rituximab had a significant reduction in both skin-related (84 % to 48 %, p = 0.01 and 81 % to 43 %, p = 0.004) and non-skin-related bleeding symptoms (p = 0.0001 and p = 0.0006) after 1 month of treatment. HRQoL significantly improved on all treatments. However, only patients treated with eltrombopag had a median improvement in KIT scores at 1 month that met the minimal important difference (MID). Bleeding, platelet count, and HRQoL improved in each treatment group, but the extent and timing of the effect varied among treatments. The authors concluded that these results are hypothesis-generating and help to improve the understanding of the effect of each treatment on specific patient outcomes. Combined with future randomized trials, these findings will help clinicians select the optimal second-line treatment for an individual child with ITP.

Furthermore, an UpToDate review on “Immune thrombocytopenia (ITP) in children: Management of chronic disease” (Bussel, 2019) states that “Splenectomy is an appropriate option for the small percentage of patients with chronic ITP who have persistent clinically significant, generally severe thrombocytopenia accompanied by hemorrhagic symptoms, who require repeated or continuous pharmacologic interventions. Although splenectomy is effective in most patients, it is also associated with substantial risks, especially overwhelming sepsis. The risk of sepsis is particularly high in very young patients (i.e., < 5 years of age), in whom splenectomy should be avoided whenever possible. Rates of splenectomy among children with ITP have declined considerably since the early 2000s, particularly among children < 5 years old. The reason for the decline is uncertain but may be related to increased availability of other effective second-line therapies. Splenectomy is effective in improving the platelet count and reducing the associated risk of bleeding in 60 to 80 % of children with chronic ITP. No universally accepted standards for the timing of splenectomy in chronic ITP exist, but the American Society of Hematology (ASH) guidelines recommend waiting until
at least 12 months after the initial ITP diagnosis, if at all possible, and avoiding splenectomy for children < 5 years old. Furthermore, there is general consensus that appropriate candidates for splenectomy are those with very low platelet counts, bleeding complications, and lack of adequate response with standard medications. When possible, surgery should be performed using a laparoscopic approach. For patients with chronic ITP whose symptoms and risks are not adequately controlled using first-line therapies and for those who remain dependent on glucocorticoid therapy to control symptoms, second-line treatment options include rituximab, thrombopoietin receptor agonists (eltrombopag, romiplostim), and splenectomy. Other agents that are sometimes used for patients who require chronic immunosuppression include azathioprine, 6-mercaptopurine, or mycophenolate mofetil. The choice among these options is complex and is highly dependent on the values and preferences of the patient and family. Splenectomy is generally reserved for patients > 5 years old who have persistent severe thrombocytopenia accompanied by clinically significant hemorrhagic symptoms and who require repeated or continuous pharmacologic interventions.”

Thrombocytopenia during Pregnancy

Decroocq et al (2014) stated that primary immune thrombocytopenia is not a rare event during pregnancy, and it must be carefully managed to avoid hemorrhagic complications for the mother. After failure of first-line treatments, the teratogenicity and toxicity of other therapeutic agents limit the available options and treatment. These investigators described the cases of 2 pregnant patients with corticosteroid-refractory immune thrombocytopenia who were successfully treated by romiplostim without any fetal or maternal complications. The authors concluded that romiplostim may represent an important alternative treatment choice during pregnancy for immune thrombocytopenia cases refractory to first-line therapy, especially because of its speed of action and high efficacy. Moreover, they stated that further data are needed to provide definitive evidence of its safety for newborns.

Furthermore, an UpToDate review on “Thrombocytopenia in pregnancy” (George and Knudtson, 2015) states that “The safety of thrombopoietin-receptor agonists (e.g., romiplostim, eltrombopag) during pregnancy is unknown”.

Thrombocytopenia following Allogeneic Stem Cell Transplantation
Maximova et al (2015) examined the outcome of romiplostim for secondary failure of platelet recovery (SFPR) in children who had undergone hematopoietic stem cell transplantation (HSCT). A total of 7 transfusion-dependent pediatric patients (median age of 11 years), with platelet counts below 10 × 10^9/L, received 4 weekly doses of subcutaneous romiplostim to treat SFPR developed after HSCT. All patients, except 1 (patient 4), became platelet transfusion-independent in the second week from the beginning of treatment and no patient needed to discontinue drug treatment because of adverse events. The authors concluded that romiplostim could represent a beneficial first-line treatment, but further studies are needed.

Furthermore, an UpToDate review on “Hematopoietic support after hematopoietic cell transplantation” (Negrin, 2015) states that “With the approval of the thrombopoietic growth factors romiplostim and eltrombopag, additional studies are needed in the HCT setting to determine if these agents can effectively stimulate platelet production, reduce bleeding risks, and reduce transfusional requirements for platelets”.

Lancman and colleagues (2018) stated that thrombocytopenia is a relatively common complication following allogeneic HSCT and is associated with increased bleeding, transfusion requirements, chronic GVHD, and all-cause mortality. There are currently no approved treatments outside of supportive transfusions. These investigators reported on the outcomes of 5 patients at their institution who received romiplostim for either primary engraftment failure or secondary failure of platelet recovery following SCT. In total, 4 of the 5 patients demonstrated a response to romiplostim, which was defined as 7 consecutive days of platelet count of greater than 50 × 10^9/L with transfusion independence, with 2 ongoing responses (greater than 365 days each) at the conclusion of the study period. Responses to romiplostim were sustained in the absence of significant bone marrow disease, which was found to contribute to recurrent thrombocytopenia. Additionally, romiplostim was well-tolerated overall; 1 patient developed minimal fibrotic changes on bone marrow biopsy post-romiplostim. The authors concluded that although these findings were promising, data from randomized clinical trials are needed to fully understand the role of romiplostim after SCT.

Therapy-Related Thrombocytopenia
Jacobson and colleagues (2017) stated that therapy-related thrombocytopenia (TRT), due to chemotherapy and/or radiation therapy, is common with pediatric cancer treatments, and it can result in dose reductions and therapy delays. Romiplostim is effective as a 2nd-line treatment for immune thrombocytopenia in children; however, there are no data for its use for TRT in children. These researchers reported a case series of 5 children treated for solid tumors where romiplostim was used without adverse effects to successfully resolve and prevent therapy-limiting refractory TRT. The authors concluded that prospective studies on this use of romiplostim are needed.

Appendix

Romiplostim (Nplate) for injection is available as 250 mcg or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials.

After initial dose, the dose is adjusted based on platelet response, using the lowest dose to achieve and maintain a platelet count greater than or equal to 50 x 10⁹/L as necessary to reduce the risk for bleeding. In the clinical trials, subjects received single weekly subcutaneous injections of Nplate, with individual dose adjustments to maintain platelet counts of 50 x 10⁹/L to 200 x 10⁹/L.

Romiplostim should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum weekly dose of 10 mcg/kg.

Romiplostim may be used with other ITP therapies, such as corticosteroids, danazol, azathioprine, intravenous immunoglobulin, and anti-D immunoglobulin.

Some studies have suggested that romiplostim may be reduced or discontinued in select persons if the member’s platelet count is 50 x 10⁹/L or greater. However, it should be noted that discontinuing Nplate therapy may result in a sudden drop in platelet count, thus, appropriate monitoring should be employed (Amgen, 2018; Vishnu and Aboulafia, 2016).

Recommended Dosing Adjustments for Adults
The initial dose of romiplostim (Nplate) is 1 mcg/kg with future dose adjustments based on changes in platelet counts only. Once-weekly dose is adjusted by increments of 1 mcg/kg, not to exceed 10 mcg/kg per week, to achieve a platelet count of greater than or equal to 50 x 10^9/L as necessary to reduce the risk for bleeding. In clinical studies, most adults who responded to romiplostim achieved and maintained platelet counts greater than or equal to 50 x 10^9/L with a median dose of 2 mcg/kg.

- If the platelet count is < 50 × 10^9/L, increase the dose by 1 mcg/kg.
- If platelet count is > 200 × 10^9/L and ≤ 400 × 10^9/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is > 400 × 10^9/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 × 10^9/L, resume Nplate at a dose reduced by 1 mcg/kg.

**Recommended Dosing Adjustments for Pediatrics (1 year to 17 years)**

The initial dose of romiplostim (Nplate) is 1 mcg/kg with future dose adjustments based on changes in platelet counts and changes in body weight. Reassessment of body weight is recommended every 12 weeks.

It is recommended that the weekly dose of Nplate be adjusted by increments of 1 mcg/kg until the pediatric member achieves a platelet count ≥ 50 × 10^9/L as necessary to reduce the risk for bleeding, not to exceed a maximum weekly dose of 10 mcg/kg. In a pediatric placebo-controlled clinical study, the median dose was 5.5 mcg/kg.

- If the platelet count is < 50 × 10^9/L, increase the dose by 1 mcg/kg.
- If platelet count is > 200 × 10^9/L and ≤ 400 × 10^9/L for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is > 400 × 10^9/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 × 10^9/L, resume Nplate at a dose reduced by 1 mcg/kg.

Source: (Amgen, 2018)

**The International Prognostic Scoring System**
Prognosis of individuals with MDS can be calculated using a number of scoring systems. There are 3 main prognostic scoring systems used in MDS:

- IPSS (International Prognostic Scoring System)
- IPSS-R (Revised International Prognostic Scoring System)
- WPSS (WHO classification-based Prognostic Scoring System)

The IPSS is a commonly used tool in MDS which uses prognostic indicators to assign a risk score, and risk group, to help predict the course of disease. The risk group information can be used to choose a treatment approach. Lower-risk MDS tends to grow and progress slowly, thus, a lower-risk score generally indicates a better outlook. The IPSS-R covers the same disease factors as the IPSS, but the factors are identified in a more detailed way. The WPSS it is not used as often as the IPPS and IPSS-R. It differs from the other two systems in that it includes the MDS subtype as a prognostic factor. It also assigns a score based on the presence or absence of severe anemia.


Examples of risk factors for bleeding (not all inclusive):

- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (e.g., peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession (construction worker) or lifestyle (e.g., plays contact sports) that predispose member to trauma.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38100 - 38120</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>96372, 96374, 96375, 96376, 96379</td>
<td>Therapeutic, prophylactic, or diagnostic injection</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J2796</td>
<td>Injection, romiplostim, 10 mcg [Nplate]</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

Doptelet (avatrombopag), mupleta (lusutrombopag), Spleen tyrosine kinase inhibitors (e.g., Tavalisse) - no specific code:

<table>
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<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>J2355</td>
<td>Injection, oprelvekin, 5mg</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D46.22, D46.c, D46.9</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>D69.3</td>
<td>Immune thrombocytopenic purpura [idiopathic]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>B17.10 - B17.11</td>
<td>Acute hepatitis C</td>
</tr>
<tr>
<td>B18.2</td>
<td>Chronic viral hepatitis C</td>
</tr>
<tr>
<td>B19.20 - B19.21</td>
<td>Unspecified viral hepatitis C</td>
</tr>
<tr>
<td>D69.0 - D69.2</td>
<td>Purpura and other hemorrhagic conditions [thrombocytopenia]</td>
</tr>
<tr>
<td>D69.41 - D69.9</td>
<td>associated with Evans syndrome</td>
</tr>
<tr>
<td>D75.81</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>D75.82</td>
<td>Heparin-induced thrombocytopenia (HIT)</td>
</tr>
<tr>
<td>D89.810 - D89.813</td>
<td>Graft-versus-host disease [associated with thrombocytopenia]</td>
</tr>
<tr>
<td>M31.1</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>O72.3</td>
<td>Postpartum coagulation defects</td>
</tr>
<tr>
<td>O36.821+ - O36.829+</td>
<td>Fetal anemia and thrombocytopenia</td>
</tr>
<tr>
<td>O99.110 - O99.119</td>
<td>Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy [thrombocytopenia]</td>
</tr>
<tr>
<td>P61.0</td>
<td>Transient neonatal thrombocytopenia</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


25. Ware RE. Autoimmune hemolytic anemia in children. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2012.


27. Chao NJ. Treatment of chronic graft-versus-host disease. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2012b.


40. Negrin RS. Hematopoietic support after hematopoietic cell transplantation. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed July 2015.


56. Estey EH, Schrier SL. Management of the complications of the myelodysplastic syndromes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2019.

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0768 Romiplostim (Nplate)

For the Pennsylvania Medical Assistance Plan, effective 1/1/20 medication coverage requests for medications on the statewide preferred drug list will be reviewed using the guidelines for determination of medical necessity developed by the Pennsylvania Department of Human Services.