Aetna considers romiplostim (Nplate™) medically necessary for the treatment of thrombocytopenia in members with chronic immune (idiopathic) thrombocytopenic purpura (ITP) whose degree of thrombocytopenia (platelet count less than 30,000/mm3) and clinical condition (active bleeding or risk factors for bleeding (such as, but not limited to, hypertension, peptic ulcer disease, anticoagulation, recent surgery, head trauma)) increases the risk for bleeding and who have had an insufficient response to corticosteroids (eg, prednisone, methylprednisolone, dexamethasone) or immunoglobulins (IVIG, anti-D (WinRho)).

Aetna considers carfilzomib injection experimental and investigational and therefore not medically necessary for the treatment of the following:

- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use.”

Background

Romiplostim (Nplate™, Amgen, Inc., Thousand Oaks, CA), a thrombopoietin receptor agonist that stimulates bone marrow megakaryocytes to produce platelets, 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 romplostim versus none (0/21) of the placebo patients, and by 61 % (25/41) of the non-splenectomized patients given romplostim 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.

The recommended initial dose of romiplostim is 1 mcg/kg as a subcutaneous injection; then as a once-weekly dose adjusted by increments of 1 mcg/kg, not to exceed 10 mcg/kg per week, to achieve a platelet count of greater than 50,000/mcL as necessary to reduce the risk for bleeding. In clinical studies, most patients who responded to romiplostim achieved and maintained platelet counts of 50 x 10(9)/L or more with a median dose of 2 mcg/kg.
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. If the patient's platelet count is 50 x 10^9/L or greater, medical ITP therapies may be reduced or discontinued.

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 10^9/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 10^9/L at baseline to 60, 73, 38, and 58 x 10^9/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.

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.

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.

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.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96372, 96374, Therapeutic, prophylactic, or diagnostic injection
96375
96376, 96379

HCPCS codes covered if selection criteria are met:

J2796 Injection, romiplostim, 10 micrograms

ICD-9 codes covered if selection criteria are met:
287.31 Immune thrombocytopenic purpura [idiopathic] [in members whose degree of thrombocytopenia and clinical condition increases the risk for bleeding and who have had an insufficient response to corticosteroids or immunoglobulins]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

070.41, 070.44, 070.51, 070.54, 070.70 - 070.71

238.73 - 238.75

279.50 - 279.53

287.0 - 287.30, 287.32 - 287.9

289.83 Myelofibrosis

289.84 Heparin-induced thrombocytopenia (HIT)

446.6 Thrombotic microangiopathy

666.30 - 666.34

678.00 - 678.03

776.1 Transient neonatal thrombocytopenia

The above policy is based on the following references:


25. Ware RE. Autoimmune hemolytic anemia in children. Last reviewed July 2012. UpToDate Inc. Waltham, MA.
27. Chao NJ. Treatment of chronic graft-versus-host disease. Last reviewed July 2012b. UpToDate Inc. Waltham, MA.