

Nplate (Romiplostim) January 2009

Nplate is a thrombopoietin receptor agonist indicated 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.

Safety?

- ❑ *Drug interactions:* Drug interactions have not been reported, however, formal drug interaction studies were not performed.
- ❑ *Look-alike/sound-alike drugs:* None.
- ❑ *Renal/Hepatic adjustment:* Romiplostim was not studied in patients with renal or hepatic function impairment; use with caution in these populations.
- ❑ *Pediatric:* The safety and effectiveness have not been established in children.
- ❑ *Elderly:* No overall differences in safety or efficacy have been observed between older or younger patients in studies. In general, dose adjustment for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- ❑ *Pregnancy Category:* Category C. In animal studies, adverse fetal effects included thrombocytosis, postimplantation loss, and an increase in pup mortality. It is not known if romiplostim is excreted in human milk. Use in breast-feeding mothers is not recommended.
- ❑ *Contraindications:* None.
- ❑ *Precautions/Warnings:* Romiplostim administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Discontinuation of romiplostim therapy may result in worsened thrombocytopenia than was present prior to therapy. Excessive romiplostim doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications. Romiplostim may increase the risk for hematologic malignancies, especially in patients with myelodysplastic syndrome. Assess patients for the formation of neutralizing antibodies if platelet counts decline after response to therapy

Tolerability =

- ❑ The most common adverse reactions observed during romiplostim therapy have included arthralgia, dizziness, headache, insomnia, myalgia, extremity pain, abdominal pain, shoulder pain, dyspepsia, and paresthesia.
- ❑ Serious adverse reactions related to romiplostim have included severe headache, elevated serum lactic dehydrogenase, elevated bone marrow reticulin, reticulin fibrosis, thrombosis, bleeding, unacceptably high platelet count, and thrombocytopenia.

Efficacy?

The safety and efficacy of romiplostim were assessed in two-double-blind, placebo-controlled studies involving patients with chronic ITP who had completed at least one prior treatment (including corticosteroids, immunoglobulins or rituximab) and had a platelet count of $\leq 30 \times 10^9$ per L before study entry. Patients received weekly injections of romiplostim (1 mcg/kg subcutaneously), with individual dose adjustments to maintain platelet counts between 50×10^9 per L and 200×10^9 per L. The primary efficacy end point was durable platelet response, defined as the achievement of a weekly platelet count $\geq 50 \times 10^9$ per L for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication.

- ❑ *Study 1* evaluated 62 patients who had not undergone a splenectomy. The mean baseline platelet count was 18.3×10^9 per L. A durable platelet response was achieved in 25 of 41 (61%) patients in the romiplostim group compared with 1 of 21 (4.8%) in the placebo group ($P < 0.0001$). Overall response, defined as either durable or transient platelet response (at least 4 weekly

platelet responses) was achieved in 36 of 41 (87.8%) patients in the romiplostim group compared with 3 of 21 (14.3%) in the placebo group. The mean number of weekly platelet responses (platelet count at least 50×10^9 per L) was greater in the romiplostim group (15.2 per 24 weeks, 63%) than the placebo group (1.3 per 24 weeks, 5%; $P < 0.0001$). Rescue medications, defined as an increase from baseline in dose of concurrent medication or use of new medication to increase platelet counts, were administered to 13 of 21 (61.9%) patients in the placebo group compared with 7 of 41 (17.1%) in the romiplostim group ($P = 0.0004$).

- *Study 2* evaluated 63 patients who had undergone a splenectomy. The mean baseline platelet count was 14.7×10^9 per L. Response was achieved in 16 of 42 (38.1%) patients in the romiplostim group compared with none in the placebo group ($P = 0.0013$). Overall response, defined as durable or transient platelet response (4 or more weekly platelet responses), occurred in 78.6% of the patients treated with romiplostim compared with none in the placebo group ($P < 0.0001$). The mean number of weekly platelet responses (platelets at least $50,000/\text{mm}^3$) was 12.3 of 24 (51%) weeks in the romiplostim group compared with 0.2 of 24 (1%; $P < 0.0001$) weeks for placebo. Rescue medications, defined as an increase from baseline in dose of concurrent medication or use of new medication to increase platelet counts, were administered to 12 of 21 (57.1%) patients in the placebo group compared with 11 of 42 (26.2%) in the romiplostim group ($P = 0.0175$). Concurrent ITP medications were discontinued or reduced by 25% in 12 of 12 patients in the romiplostim group compared with 1 of 6 (16.7%) in the placebo group.

Results of the 2 phase 3 studies were combined for analysis of bleeding events. The total numbers of bleeding events were 76 in the 42 placebo-treated patients and 152 in the 83 romiplostim-treated patients, corresponding to an exposure-adjusted incidence of 7.9 and 7.8, respectively, per 100 patient-weeks. The incidence was further reduced to 5.2 per 100 patient-weeks in the romiplostim-treated patients when their platelet counts were 50×10^9 per L, or more. Clinically significant bleeding (Medical Dictionary for Regulatory Activities [MedDRA] 9.0–defined severity grade 3 or higher) did not occur in responding patients and was reported only when platelet counts were less than 20×10^9 per L. Among nonresponders, there were 5 significant bleeding events in placebo patients and 10 in romiplostim patients, corresponding to an adjusted incidence of 0.5 per 100 patient-weeks in each group.

Price =/- (dose dependent)

Generic Name	Usual Dose ^a	Acquisition Cost ^b	Acquisition Cost for 30-day Supply ^b
Romiplostim	1 mcg/kg/week (dose adjusted weekly based on platelet count)	\$\$\$\$ (250 mcg minimum vial size)	\$\$\$\$
Prednisone	1-2 mg/kg/day	\$	\$
Immune Globulin	1-2 gm/kg	\$\$\$\$\$\$\$\$	Additional doses may be necessary based on platelet response
Rho(D) Immune Globulin	50 mcg/kg	\$\$\$\$\$\$	Additional doses (25-60 mcg/kg) may be necessary based on platelet response

^aCost calculated based on 80 kg patient

^bCost based on lowest usual dose

Simplicity -

- ❑ Romiplostim is only available through a restricted distribution program called Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program.
- ❑ Romiplostim is available in 250 mcg and 500 mcg single dose vials for reconstitution. The vial requires refrigeration. Once reconstituted the solution is stable for up to 24 hours at room temperature or refrigerated. The reconstituted product must be protected from light.
- ❑ The final concentration is 500 mcg. per ml. Use a syringe with graduations to 0.01 ml, as the injection volume may be very small.
- ❑ Recommended monitoring: Complete blood cell counts, including platelet counts and peripheral blood smears, should be monitored prior to the initiation of therapy, weekly until a stable romiplostim dose has been achieved, and at least monthly thereafter. The peripheral blood smear should be closely examined prior to initiation of therapy to establish a baseline level of cellular morphologic abnormalities.
- ❑ Dosing: The initial dose is 1 mcg/kg (actual body weight) subcutaneously once weekly. The dose may be adjusted weekly by increments of 1 mcg/kg to achieve and maintain a platelet count of $50 \times 10^9/L$ or more as necessary to reduce bleeding risk.
- ❑ Monitor complete blood cell counts, including platelet counts for at least 2 weeks following romiplostim discontinuation (for worsening thrombocytopenia).

Recommendations

- ❑ The FDA has required Amgen to conduct the following postmarketing evaluations:
 1. Collect follow-up platelet counts and other clinical data sufficient to assess the long-term consequences of the detected antibodies.
 2. Develop and maintain a prospective, observational pregnancy exposure registry study.
 3. Evaluate the presence of romiplostim in breast milk of lactating women and determine if there is any effect on milk production and composition.
 4. Phase IV study to evaluate the changes in bone marrow morphology in subjects receiving romiplostim for the treatment of ITP. It is designed to detect the development of antibody formation and cardiac conduction abnormalities.
- ❑ The drug is generally well tolerated, and only a few patients have developed antibodies to the medication.
- ❑ It will be important to determine if the development of romiplostim antibodies is associated with decreased efficacy in patients requiring chronic administration of this medication to maintain control of their disease.
- ❑ Romiplostim appears to be well-tolerated in ITP patients and reduced the incidence of bleeding events among patients exhibiting a platelet response.

References

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