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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Nplate safely and effectively. See [full prescribing information](#) for Nplate.

### Nplate™ (romiplostim)

#### For subcutaneous injection

Initial U.S. Approval: 2008

#### INDICATIONS AND USAGE

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.

Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Nplate should not be used in an attempt to normalize platelet counts. (1)

#### DOSAGE AND ADMINISTRATION

- Initial dose of 1 mcg/kg once weekly as a subcutaneous injection. (2.1)
- Adjust weekly dose by increments of 1 mcg/kg to achieve and maintain a platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding. (2.1)
- Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelet count is  $> 400 \times 10^9/L$ . (2.1)
- Discontinue Nplate if platelet count does not increase after 4 weeks at the maximum dose. (2.1)
- Do not shake during reconstitution; protect reconstituted Nplate from light; administer reconstituted Nplate within 24 hours. (2.2)
- The injection volume may be very small. Use a syringe with graduations to 0.01 mL. (2.2)
- Discard any unused portion of the single-use vial. (2.2)

#### DOSAGE FORMS AND STRENGTHS

- 250 mcg or 500 mcg of deliverable romiplostim in single-use vials (3)

#### CONTRAINDICATIONS

- None (4)

#### WARNINGS AND PRECAUTIONS

- Nplate increases the risk for reticulin deposition within the bone marrow; clinical studies have not ruled out the possibility that reticulin and other fiber deposition may result in bone marrow fibrosis with cytopenias. Monitor peripheral blood for signs of marrow fibrosis. (5.1)

- Discontinuation of Nplate may result in worsened thrombocytopenia than was present prior to Nplate therapy. Monitor complete blood counts (CBCs), including platelet counts, for at least 2 weeks following Nplate discontinuation. (5.2)
- Excessive Nplate doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications. (5.3)
- Assess patients for the formation of neutralizing antibodies if platelet counts importantly decrease following an initial Nplate response. (5.4)
- Nplate may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome. (5.5)
- Monitor CBCs, including platelet counts and peripheral blood smears, weekly until a stable Nplate dose has been achieved. Thereafter, monitor CBCs, including platelet counts and peripheral blood smears, at least monthly. (5.6)
- Nplate is available only through a restricted distribution program called the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. Under the Nplate NEXUS Program, only prescribers and patients registered with the program are able to prescribe, administer, and receive product. To enroll in the Nplate NEXUS Program, call 1-877-Nplate1 (1-877-675-2831). (5.7)

#### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 5\%$  higher patient incidence in Nplate versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia. Headache was the most commonly reported adverse reaction that did not occur at  $\geq 5\%$  higher patient incidence in Nplate versus placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-877-Nplate1 (1-877-675-2831) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, Nplate may cause fetal harm. Enroll pregnant patients in the Nplate pregnancy registry by calling 1-877-Nplate1 (1-877-675-2831). (8.1)
- Nursing Mothers: A decision should be made to discontinue Nplate or nursing, taking into account the importance of Nplate to the mother. (8.3)

See 17 FOR PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 08/2008

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Nplate is 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. 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.

### 2 DOSAGE AND ADMINISTRATION

Only prescribers enrolled in the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program may prescribe Nplate [*see Warnings and Precautions (5.7)*]. Nplate must be administered by the enrolled prescribers or healthcare providers under their direction.

#### 2.1 Recommended Dosage Regimen

Monitor complete blood counts (CBCs), including platelet counts and peripheral blood smears, prior to initiation of Nplate and throughout Nplate therapy. Monitor CBCs, including platelet counts, for at least 2 weeks following discontinuation of Nplate [*see Warnings and Precautions (5.6)*].

Use the lowest dose of Nplate to achieve and maintain a platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding. Administer Nplate as a weekly subcutaneous injection with dose adjustments based upon the platelet count response. Nplate should not be used in an attempt to normalize platelet counts [*see Warnings and Precautions (5.3)*].

The prescribed Nplate dose may consist of a very small volume (eg, 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  $\geq 50 \times 10^9/L$  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  $\geq 50 \times 10^9/L$  with a median dose of 2 mcg/kg.

During Nplate therapy, assess CBCs, including platelet count and peripheral blood smears, weekly until a stable platelet count ( $\geq 50 \times 10^9/L$  for at least 4 weeks without dose adjustment) has been achieved. Obtain CBCs, including platelet counts and peripheral blood smears, monthly thereafter.

Adjust the dose as follows:

- If the platelet count is  $< 50 \times 10^9/L$ , increase the dose by 1 mcg/kg.
- If platelet count is  $> 200 \times 10^9/L$  for 2 consecutive weeks, reduce the dose by 1 mcg/kg.
- If platelet count is  $> 400 \times 10^9/L$ , do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to  $< 200 \times 10^9/L$ , 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 [*see Warnings and Precautions (5.4)*]. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate [*see Warnings and Precautions (5.6)*].

## 2.2 Preparation and Administration

Nplate is supplied in single-use vials as a sterile, preservative-free, white lyophilized powder that must be reconstituted as outlined in Table 1 and administered using a syringe with 0.01 mL graduations. Using aseptic technique, reconstitute Nplate with preservative-free Sterile Water for Injection, USP as described in Table 1. Do not use bacteriostatic water for injection.

**Table 1. Reconstitution of Nplate Single-Use Vials**

Nplate Single-Use Vial	Total Vial Content of Romiplostim		Sterile Water for Injection*	=	Deliverable Product and Volume	Final Concentration
250 mcg	375 mcg	add	0.72 mL	=	250 mcg in 0.5 mL	500 mcg/mL
500 mcg	625 mcg	add	1.2 mL	=	500 mcg in 1 mL	500 mcg/mL

\* Use preservative-free Sterile Water for Injection.

Gently swirl and invert the vial to reconstitute. Avoid excess or vigorous agitation: **DO NOT SHAKE**. Generally, dissolution of Nplate takes less than 2 minutes. The reconstituted Nplate solution should be clear and colorless. Visually inspect the reconstituted solution for particulate matter and/or discoloration. Do not administer Nplate if particulate matter and/or discoloration is observed.

Reconstituted Nplate can be kept at room temperature (25°C/77°F) or refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours prior to administration. Protect the reconstituted product from light.

To determine the injection volume to be administered, first identify the patient’s total dose in micrograms (mcg) using the dosing information in Section 2.1. For example, a 75 kg patient initiating therapy at 1 mcg/kg will begin with a dose of 75 mcg. Next, calculate the volume of Nplate solution that is given to the patient by dividing the microgram dose by the concentration of the reconstituted Nplate solution (500 mcg/mL). For this patient example, the 75 mcg dose is divided by 500 mcg/mL, resulting in an injection volume of 0.15 mL.

As the injection volume may be very small, use a syringe with graduations to 0.01 mL.

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.

## 2.3 Use of Nplate With Concomitant Medical ITP Therapies

Nplate may be used with other medical ITP therapies, such as corticosteroids, danazol, azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. If the patient’s platelet count is  $\geq 50 \times 10^9/L$ , medical ITP therapies may be reduced or discontinued [see *Clinical Studies (14.1)*].

## 3 DOSAGE FORMS AND STRENGTHS

Single-use vials contain 250 or 500 mcg of deliverable romiplostim as a sterile, lyophilized, solid white powder.

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. In clinical studies, Nplate was discontinued in four of the 271 patients because of bone marrow reticulin deposition. Six additional patients had reticulin observed upon bone marrow biopsy. All 10 patients with bone marrow reticulin deposition had received Nplate doses  $\geq 5$  mcg/kg and six received doses  $\geq 10$  mcg/kg. Progression

to marrow fibrosis with cytopenias was not reported in the controlled clinical studies. In the extension study, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

Prior to initiation of Nplate, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable Nplate dose, examine peripheral blood smears and CBCs monthly for new or worsening morphological abnormalities (eg, teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Nplate and consider a bone marrow biopsy, including staining for fibrosis [see *Adverse Reactions (6.1)*].

## **5.2 Worsened Thrombocytopenia After Cessation of Nplate**

Discontinuation of Nplate may result in thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if Nplate is discontinued while the patient is on anticoagulants or antiplatelet agents. In clinical studies of patients with chronic ITP who had Nplate discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia resolved within 14 days. Following discontinuation of Nplate, obtain weekly CBCs, including platelet counts, for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines [see *Adverse Reactions (6.1)*].

## **5.3 Thrombotic/Thromboembolic Complications**

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of Nplate or medication errors that result in excessive Nplate doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was similar between Nplate and placebo. To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of  $\geq 50 \times 10^9/L$  [see *Dosage and Administration (2.1)*].

## **5.4 Lack or Loss of Response to Nplate**

Hyporesponsiveness or failure to maintain a platelet response with Nplate should prompt a search for causative factors, including neutralizing antibodies to Nplate or bone marrow fibrosis [see *Warnings and Precautions (5.1) and Adverse Reactions (6.2)*]. To detect antibody formation, submit blood samples to Amgen (1-800-772-6436). Amgen will assay these samples for antibodies to Nplate and thrombopoietin (TPO). Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the highest weekly dose of 10 mcg/kg.

## **5.5 Malignancies and Progression of Malignancies**

Nplate stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In controlled clinical studies among patients with chronic ITP, the incidence of hematologic malignancy was low and similar between Nplate and placebo. In a separate single-arm clinical study of 44 patients with myelodysplastic syndrome (MDS), 11 patients were reported as having possible disease progression, among whom four patients had confirmation of acute myelogenous leukemia (AML) during follow-up. Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

## **5.6 Laboratory Monitoring**

Monitor CBCs, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of Nplate therapy. Prior to the initiation of Nplate, examine the peripheral blood differential to establish the baseline extent of red and white blood cell abnormalities. Obtain CBCs, including platelet counts and

peripheral blood smears, weekly during the dose adjustment phase of Nplate therapy and then monthly following establishment of a stable Nplate dose. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate [see *Dosage and Administration (2.1) and Warnings and Precautions (5.1, 5.2)*].

## **5.7 Nplate Distribution Program**

Nplate is available only through a restricted distribution program called Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. Under the Nplate NEXUS Program, only prescribers and patients registered with the program are able to prescribe, administer, and receive Nplate. This program provides educational materials and a mechanism for the proper use of Nplate. To enroll in the Nplate NEXUS Program, call 1-877-Nplate1 (1-877-675-2831). Prescribers and patients are required to understand the risks of Nplate therapy. Prescribers are required to understand the information in the prescribing information and be able to:

- Educate patients on the benefits and risks of treatment with Nplate, ensure that the patient receives the Medication Guide, instruct them to read it, and encourage them to ask questions when considering Nplate. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the Nplate NEXUS Program Healthcare Provider Enrollment Form, sign the form, and return the form according to Nplate NEXUS Program instructions.
- Review the Nplate NEXUS Program Patient Enrollment Form, answer all questions, obtain the patient's signature on the Nplate NEXUS Program Patient Enrollment Form, place the original signed form in the patient's medical record, send a copy according to Nplate NEXUS Program instructions, and give a copy to the patient.
- Report any serious adverse events associated with the use of Nplate to the Nplate NEXUS Program Call Center at 1-877-Nplate1 (1-877-675-2831) or to the FDA's MedWatch Program at 1-800-FDA-1088.
- Report serious adverse events observed in patients receiving Nplate, including events actively solicited at 6-month intervals.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Studies Experience**

Serious adverse reactions associated with Nplate in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate discontinuation [see *Warnings and Precautions (5.1, 5.2)*].

The data described below reflect Nplate exposure to 271 patients with chronic ITP, aged 18 to 88, of whom 62% were female. Nplate was studied in two randomized, placebo-controlled, double-blind studies that were identical in design, with the exception that Study 1 evaluated nonsplenectomized patients with ITP and Study 2 evaluated splenectomized patients with ITP. Data are also reported from an open-label, single-arm study in which patients received Nplate over an extended period of time. Overall, Nplate was administered to 114 patients for at least 52 weeks and 53 patients for at least 96 weeks.

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Nplate and 32% of patients receiving placebo. Headaches were usually of mild or moderate severity. Table 2 presents adverse drug reactions from Studies 1 and 2 with a  $\geq 5\%$  higher patient incidence in Nplate versus placebo. The majority of these adverse drug reactions were mild to moderate in severity.

**Table 2. Adverse Drug Reactions Identified in Two Placebo-Controlled Studies**

<b>Preferred Term</b>	<b>Nplate (n = 84)</b>	<b>Placebo (n = 41)</b>
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in Extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paresthesia	6%	0%

Among 142 patients with chronic ITP who received Nplate in the single-arm extension study, the incidence rates of the adverse reactions occurred in a pattern similar to those reported in the placebo-controlled clinical studies.

## **6.2 Immunogenicity**

As with all therapeutic proteins, patients may develop antibodies to the therapeutic protein. Patients were screened for immunogenicity to romiplostim using a BIAcore-based biosensor immunoassay. This assay is capable of detecting both high- and low-affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In clinical studies, the incidence of preexisting antibodies to romiplostim was 8% (17/225) and the incidence of binding antibody development during Nplate treatment was 10% (23/225). The incidence of preexisting antibodies to endogenous TPO was 5% (12/225) and the incidence of binding antibody development to endogenous TPO during Nplate treatment was 5% (12/225). Of the patients with positive antibodies to romiplostim or to TPO, one (0.4%) patient had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No correlation was observed between antibody activity and clinical effectiveness or safety.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to romiplostim with the incidence of antibodies to other products may be misleading.

## **7 DRUG INTERACTIONS**

No formal drug interaction studies of Nplate have been performed.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no adequate and well-controlled studies of Nplate use in pregnant women. In animal reproduction and developmental toxicity studies, romiplostim crossed the placenta, and adverse fetal effects included thrombocytosis, postimplantation loss, and an increase in pup mortality. Nplate should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

***Pregnancy Registry:*** A pregnancy registry has been established to collect information about the effects of Nplate use during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the Nplate pregnancy registry by calling 1-877-Nplate1 (1-877-675-2831).

In rat and rabbit developmental toxicity studies no evidence of fetal harm was observed at romiplostim doses up to 11 times (rats) and 82 times (rabbit) the maximum human dose (MHD) based on systemic exposure. In mice at doses 5 times the MHD, reductions in maternal body weight and increased postimplantation loss occurred.

In a prenatal and postnatal development study in rats, at doses 11 times the MHD, there was an increase in perinatal pup mortality. Romiplostim crossed the placental barrier in rats and increased fetal platelet counts at clinically equivalent and higher doses.

### **8.3 Nursing Mothers**

It is not known whether Nplate is excreted in human milk; however, human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Nplate, a decision should be made whether to discontinue nursing or to discontinue Nplate, taking into account the importance of Nplate to the mother and the known benefits of nursing.

### **8.4 Pediatric Use**

The safety and effectiveness in pediatric patients (< 18 years) have not been established.

### **8.5 Geriatric Use**

Of the 271 patients who received Nplate in ITP clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out. 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.

### **8.6 Renal Impairment**

No clinical studies were conducted in patients with renal impairment. Use Nplate with caution in this population.

### **8.7 Hepatic Impairment**

No clinical studies were conducted in patients with hepatic impairment. Use Nplate with caution in this population.

## **10 OVERDOSAGE**

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In this case, discontinue Nplate and monitor platelet counts. Reinitiate treatment with Nplate in accordance with dosing and administration recommendations [*see Dosage and Administration (2.2)*].

## **11 DESCRIPTION**

Romiplostim, a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor (also known as cMpl). The peptibody molecule contains two identical single-chain subunits, each consisting of human immunoglobulin IgG1 Fc domain, covalently linked at the C-terminus to a peptide containing two thrombopoietin receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E coli*).

Nplate is supplied as a sterile, preservative-free, lyophilized, solid white powder for subcutaneous injection. Two vial presentations are available, which contain a sufficient amount of active ingredient to provide either 250 mcg or 500 mcg of deliverable romiplostim, respectively. Each single-use 250 mcg vial of Nplate contains the following: 375 mcg romiplostim, 30 mg mannitol, 15 mg sucrose, 1.2 mg L-histidine, 0.03 mg polysorbate 20, and sufficient HCl to adjust the pH to a target of 5.0. Each single-use 500 mcg vial of Nplate contains the following: 625 mcg romiplostim, 50 mg mannitol, 25 mg sucrose, 1.9 mg L-histidine, 0.05 mg polysorbate 20, and sufficient HCl to adjust the pH to a target of 5.0 [see *Dosage and Administration* (2.2)].

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Nplate increases platelet production through binding and activation of the TPO receptor, a mechanism analogous to endogenous TPO.

### **12.2 Pharmacodynamics**

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, 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  $50 \times 10^9/L$  for seven out of eight patients with chronic ITP who received six weekly doses of Nplate at 1 mcg/kg.

### **12.3 Pharmacokinetics**

In the long-term extension study in patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of romiplostim over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of romiplostim were observed about 7 to 50 hours post dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed (n = 4) after six weekly doses of Nplate (3 mcg/kg). The accumulation at higher doses of romiplostim is unknown.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of romiplostim has not been evaluated. The mutagenic potential of romiplostim has not been evaluated. Romiplostim had no effect on the fertility of rats at doses up to 37 times the MHD based on systemic exposure.

### **13.2 Animal Toxicology and/or Pharmacology**

In a 4-week repeat-dose toxicity study in which rats were dosed subcutaneously three times per week, romiplostim caused extramedullary hematopoiesis, bone hyperostosis and marrow fibrosis at clinically equivalent and higher doses. In this study, these findings were not observed in animals after a 4-week post treatment recovery period. Studies of long-term treatment with romiplostim in rats have not been conducted; therefore, it is not known if the fibrosis of the bone marrow is reversible in rats after long-term treatment.

## **14 CLINICAL STUDIES**

### **14.1 Chronic ITP**

The safety and efficacy of Nplate were assessed in two double-blind, placebo-controlled clinical studies and in an open-label extension study.

### Studies 1 and 2

In Studies 1 and 2, patients with chronic ITP who had completed at least one prior treatment and had a platelet count of  $\leq 30 \times 10^9/L$  prior to study entry were randomized (2:1) to 24 weeks of Nplate (1 mcg/kg subcutaneous [SC]) or placebo. Prior ITP treatments in both study groups included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (ie, corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage. Patients received single weekly SC injections of Nplate, with individual dose adjustments to maintain platelet counts ( $50 \times 10^9/L$  to  $200 \times 10^9/L$ ).

Study 1 evaluated patients who had not undergone a splenectomy. The patients had been diagnosed with ITP for approximately 2 years and had received a median of three prior ITP treatments. Overall, the median platelet count was  $19 \times 10^9/L$  at study entry. During the study, the median weekly Nplate dose was 2 mcg/kg (25th–75th percentile: 1–3 mcg/kg).

Study 2 evaluated patients who had undergone a splenectomy. The patients had been diagnosed with ITP for approximately 8 years and had received a median of six prior ITP treatments. Overall, the median platelet count was  $14 \times 10^9/L$  at study entry. During the study, the median weekly Nplate dose was 3 mcg/kg (25th–75th percentile: 2–7 mcg/kg).

Study 1 and 2 outcomes are shown in Table 3. A durable platelet response was the achievement of a weekly platelet count  $\geq 50 \times 10^9/L$  for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication at any time. A transient platelet response was the achievement of any weekly platelet counts  $\geq 50 \times 10^9/L$  for any 4 weeks during the treatment period without a durable platelet response. An overall platelet response was the achievement of either a durable or a transient platelet response. Platelet responses were excluded for 8 weeks after receiving rescue medications.

**Table 3. Results From Placebo-Controlled Studies<sup>a</sup>**

Outcomes	Study 1		Study 2	
	Nonsplenectomized Patients	Splenectomized Patients	Nplate	Placebo
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
<b>Platelet Responses and Rescue Therapy</b>				
Durable Platelet Response, n (%)	25 (61%)	1 (5%)	16 (38%)	0 (0%)
Overall Platelet Response, n (%)	36 (88%)	3 (14%)	33 (79%)	0 (0%)
Number of Weeks With Platelet Counts $\geq 50 \times 10^9/L$ , average	15	1	12	0
Requiring Rescue Therapy, n (%)	8 (20%)	13 (62%)	11 (26%)	12 (57%)
<b>Reduction/Discontinuation of Baseline Concurrent ITP Medical Therapy</b>				
Receiving Therapy at Baseline	(n = 11)	(n = 10)	(n = 12)	(n = 6)
Patients Who Had > 25% Dose Reduction in Concurrent Therapy, n (%)	4/11 (36%)	2/10 (20%)	4/12 (33%)	1/6 (17%)
Patients Who Discontinued Baseline Therapy, n (%) <sup>b</sup>	4/11 (36%)	3/10 (30%)	8/12 (67%)	0/6 (0%)

<sup>a</sup> All *P* values < 0.05 for platelet response and rescue therapy comparisons between Nplate and placebo.

<sup>b</sup> For multiple concomitant baseline therapies, all therapies were discontinued.

In Studies 1 and 2, nine patients reported a serious bleeding event [five (6%) Nplate, four (10%) placebo]. Bleeding events that were grade 2 severity or higher occurred in 15% of patients treated with Nplate and 34% of patients treated with placebo.

### ***Extension Study***

Patients who had participated in either Study 1 or Study 2 were withdrawn from study medications. If platelet counts subsequently decreased to  $\leq 50 \times 10^9/L$ , the patients were allowed to receive Nplate in an open-label extension study with weekly dosing based on platelet counts. Following Nplate discontinuation in Studies 1 and 2, seven patients maintained platelet counts of  $\geq 50 \times 10^9/L$ . Among 100 patients who subsequently entered the extension study, platelet counts were increased and sustained regardless of whether they had received Nplate or placebo in the prior placebo-controlled studies. The majority of patients reached a median platelet count of  $50 \times 10^9/L$  after receiving one to three doses of Nplate, and these platelet counts were maintained throughout the remainder of the study with a median duration of Nplate treatment of 60 weeks and a maximum duration of 96 weeks.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Nplate is supplied in single-use vials containing 250 mcg (NDC 55513-221-01) and 500 mcg (NDC 55513-222-01) deliverable romiplostim.

Store Nplate vials in their carton to protect from light until time of use. Keep Nplate vials refrigerated at 2° to 8°C (36° to 46°F). Do not freeze.

## **17 PATIENT COUNSELING INFORMATION**

*See FDA-Approved Medication Guide.*

### **17.1 Information for Patients**

Prior to treatment, patients should fully understand the risks and benefits of Nplate. Inform patients that the risks associated with long-term administration of Nplate are unknown and that they must enroll in the Nplate NEXUS Program, which provides for the proper use of Nplate in ITP patients.

Inform patients of the following risks and considerations for Nplate:

- Nplate can only be administered by a healthcare provider who is enrolled in the Nplate NEXUS Program or a healthcare provider under their direction.
- Nplate therapy is administered to achieve and maintain a platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding; Nplate is not used to normalize platelet counts.
- Following discontinuation of Nplate, thrombocytopenia and risk of bleeding may develop that is worse than that experienced prior to the Nplate therapy.
- Nplate therapy increases the risk of reticulin fiber formation within the bone marrow, and further fiber formation may progress to marrow fibrosis. Detection of peripheral blood cell abnormalities may necessitate a bone marrow examination.
- Too much Nplate may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.
- Nplate stimulates certain bone marrow cells to make platelets and may increase the risk for progression of underlying MDS or hematological malignancies.
- Platelet counts and CBCs, including peripheral blood smears, must be performed weekly until a stable Nplate dose has been achieved; thereafter, platelet counts and CBCs, including peripheral blood smears, must be performed monthly while taking Nplate.
- Patients must be closely monitored with weekly platelet counts and CBCs for at least 2 weeks following Nplate discontinuation.
- Even with Nplate therapy, patients should continue to avoid situations or medications that may increase the risk for bleeding.

### **17.2 FDA-Approved Medication Guide**



Nplate™ (romiplostim)

**Manufactured by:**

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more U.S. Patents, including U.S. Patent Nos. 6,835,809 and 7,189,827, as well as other patents or patents pending.

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