

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 injection, for subcutaneous use
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

- Indications and Usage (1) 12/2018
- Dosage and Administration (2.1, 2.2, 2.3) 12/2018

INDICATIONS AND USAGE

Nplate is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in:

- Adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP.
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- Nplate should not be used in an attempt to normalize platelet counts. (1)

DOSAGE AND ADMINISTRATION

- Recommended Initial Dose: 1 mcg/kg once weekly as a subcutaneous injection. Adjust dose based on platelet response. (2.1)
- See Full Prescribing Information for instructions on reconstitution, preparation, and administration. (2.2)

DOSAGE FORMS AND STRENGTHS

- For injection: 250 mcg or 500 mcg of deliverable romiplostim as a lyophilized powder in single-dose vials. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- In some patients with MDS, Nplate increases blast cell counts and increases the risk of progression to acute myelogenous leukemia. (5.1)
- Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate. (5.2)
- If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralizing antibodies. (5.3)

ADVERSE REACTIONS

- In adult patients, the most common adverse reactions (≥ 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 ≥ 5% higher patient incidence in Nplate versus placebo. (6.1)
- In pediatric patients, the most common adverse reactions (≥ 25%) are: contusion, upper respiratory tract infection, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, Nplate may cause fetal harm. (8.1)
- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Nplate is indicated for the treatment of thrombocytopenia in:

- Adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Limitations of Use:

- Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP [see *Warnings and Precautions (5.1)*].
- Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding [see *Warnings and Precautions (5.2)*].
- Nplate should not be used in an attempt to normalize platelet counts [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

For All Patients

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.

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

See Section 2.3 for monitoring recommendations during Nplate therapy.

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 (5.3)*].

For Adult Patients with Chronic ITP

The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of treatment should always be used when calculating the initial dose. In adults, future dose adjustments are based on changes in platelet counts only.

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 adult patients who responded to Nplate achieved and maintained platelet counts $\geq 50 \times 10^9/L$ with a median dose of 2 mcg/kg.

Adjust the dose as follows for adult patients:

- If the platelet count is $< 50 \times 10^9/L$, increase the dose by 1 mcg/kg.
- If platelet count is $> 200 \times 10^9/L$ and $\leq 400 \times 10^9/L$ 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.

For Pediatric Patients with ITP

The initial dose of Nplate is 1 mcg/kg. Actual body weight at initiation of treatment should always be used when calculating initial dose. In pediatric patients, future dose adjustments are based on changes in platelet counts and changes in body weight. Reassessment of body weight is recommended every 12 weeks.

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 a pediatric placebo-controlled clinical study, the median dose was 5.5 mcg/kg.

Adjust the dose as follows for pediatric patients:

- If the platelet count is $< 50 \times 10^9/L$, increase the dose by 1 mcg/kg.
- If platelet count is $> 200 \times 10^9/L$ and $\leq 400 \times 10^9/L$ 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.

2.2 Preparation and Administration

To mitigate against medication errors (both overdose and underdose), ensure that these preparation and administration instructions are followed. Use aseptic technique. Only administer subcutaneously [see *Overdosage (10)*].

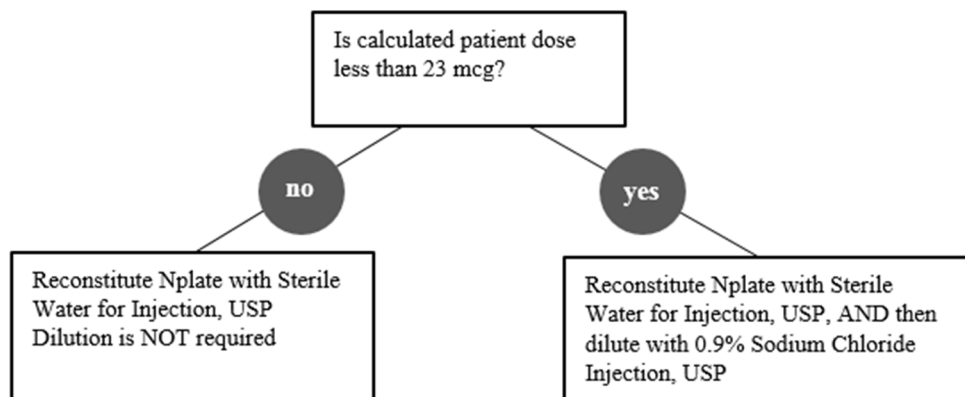
Nplate is supplied in single-dose vials as a sterile, preservative-free, white lyophilized powder that must be reconstituted as outlined in Table 1 and administered using a syringe with 0.01 mL graduations.

Calculation of Patient Dose

Multiply the patient's weight (kg) by the prescribed dose to obtain the Calculated Patient Dose.

$\text{Calculated Patient Dose (mcg)} = \text{Weight (kg)} \times \text{Prescribed dose (mcg/kg)}$
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Reconstitution and Dilution of Nplate Single-Dose Vials



Reconstitute Nplate with Sterile Water for Injection, USP. If the Calculated Patient Dose is less than 23 mcg, dilution with 0.9% Sodium Chloride Injection, USP is required. Follow instructions in Table 1.

Table 1. Reconstitution and Dilution of Nplate Single-Dose Vials

Calculated Patient Dose	Labeled Vial Content of Nplate	Actual Vial Content of Nplate*	Reconstitute with Sterile Water**	Dilute with Normal Saline***	Final Concentration
Calculated Dose greater than or equal to 23 mcg	250 mcg	375 mcg	0.72 mL	Not Required	500 mcg/mL
	500 mcg	625 mcg	1.2 mL	Not Required	
Calculated Dose less than 23 mcg	250 mcg	375 mcg	0.72 mL	2.25 mL	125 mcg/mL
	500 mcg	625 mcg	1.2 mL	3.75 mL	

* Actual vial content includes overfill to ensure delivery of calculated dose.

** Add Sterile Water for Injection, USP directly to the vial.

*** Add 0.9% Sodium Chloride Injection, USP directly to the vial.

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.

Initial reconstitution of Nplate with designated volumes of Sterile Water for Injection, USP results in a concentration of 500 mcg/mL in all vial sizes. **Do not** reconstitute or dilute with Bacteriostatic Water for Injection, USP or dilute with Bacteriostatic Sodium Chloride Injection, USP.

If a patient's dose is less than 23 mcg, then additional dilution with 0.9% Sodium Chloride Injection, USP is required. Dilution per reconstitution instructions results in reducing the concentration of Nplate from 500 mcg/mL to 125 mcg/mL in all vial sizes (see Table 1). This reduced concentration allows for low-doses to be accurately calculated, and consistently measured with a 0.01 mL graduated syringe.

Administration of Prepared Nplate Solution

Calculate Volume to Administer by dividing the Calculated Patient Dose (mcg) by the final concentration. See Table 2 for final concentrations.

Table 2. Administration of Prepared Nplate Solution

Calculated Patient Dose	Final Concentration	Volume to Administer (mL)
Calculated Dose greater than or equal to 23 mcg	500 mcg/mL	= Calculated Patient Dose / 500 mcg/mL
Calculated Dose less than 23 mcg	125 mcg/mL	= Calculated Patient Dose / 125 mcg/mL

Administer Nplate only using a syringe with 0.01 mL graduations for accurate dosage. Round volume to the nearest hundredth mL. Verify that the syringe contains the correct dosage.

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

Storage of Reconstituted Solution

Reconstituted product with Sterile Water for Injection, USP that has not been further diluted can remain in the original vial at room temperature 25°C (77°F) or be refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours

following reconstitution. Reconstituted product with Sterile Water for Injection, USP may be held in a syringe at room temperature 25°C (77°F) for a maximum of 4 hours following reconstitution. Protect product from light. Do not shake.

Storage of Diluted solution (after initial reconstitution)

Reconstituted and further diluted product with 0.9% Sodium Chloride Injection, USP can be held in a syringe at room temperature 25°C (77°F) or in the original vial refrigerated at 2°C to 8°C (36°F to 46°F) for no longer than 4 hours prior to administration. Protect product from light. Do not shake.

2.3 Monitoring to Assess Effectiveness and Safety

Obtain CBCs, including platelet counts, 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)*].

3 DOSAGE FORMS AND STRENGTHS

For injection: 250 mcg or 500 mcg of deliverable Nplate as a sterile, lyophilized, solid white powder in single-dose vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Progression of Myelodysplastic Syndromes to Acute Myelogenous Leukemia

Progression from myelodysplastic syndromes (MDS) to acute myelogenous leukemia (AML) has been observed in adult clinical trials with Nplate.

A randomized, double-blind, placebo-controlled trial enrolling adult patients with severe thrombocytopenia and International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS was terminated due to more cases of AML observed in the Nplate arm. This trial consisted of a 58-week study period with a 5-year long-term follow-up phase. The subjects were randomized 2:1 to treatment with Nplate or placebo (167 Nplate, 83 placebo). During the 58-week study period, progression to AML occurred in 10 (6.0%) subjects in the Nplate arm and 4 (4.8%) subjects in the placebo arm (hazard ratio [95%CI] = 1.20 [0.38, 3.84]). Of the 250 subjects, 210 (84.0%) entered the long-term follow-up phase of this study. With 5-years of follow-up, 29 (11.6%) subjects showed progression to AML, including 20/168 (11.9%) subjects in the Nplate arm versus 9/82 (11.0%) subjects in the placebo arm (HR [95% CI] = 1.06 [0.48, 2.33]). The incidence of death (overall survival) was 55.7% (93/167) in the Nplate arm versus 54.2% (45/83) in the placebo arm (HR [95% CI] = 1.03 [0.72, 1.47]). In the baseline low IPSS group, there was a higher incidence of death in the Nplate arm [41.3% (19/46)] compared to the placebo arm [30.4% (7/23)] [HR (95% CI) = 1.59 (0.67, 3.80)].

In a single-arm trial of Nplate given to 72 subjects with thrombocytopenia-related MDS, 8 (11.1%) subjects were reported as having possible disease progression, of which 3 (4.2%) had confirmation of AML during follow-up. In addition, in 3 (4.2%) subjects, increased peripheral blood blast cell counts decreased to baseline after discontinuation of Nplate.

Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

5.2 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from increases in platelet counts with Nplate use. Portal vein thrombosis has been reported in patients with chronic liver disease receiving Nplate.

To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate in an attempt to normalize platelet counts. Follow the dose adjustment guidelines [see *Dosage and Administration (2.1)*].

5.3 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 [see *Adverse Reactions (6.3)*]. 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:

- Progression of Myelodysplastic Syndromes [see *Warnings and Precautions (5.1)*]
- Thrombotic/Thromboembolic Complications [see *Warnings and Precautions (5.2)*]
- Loss of Response to Nplate [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials 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.

Adults

The data described below reflect Nplate exposure to 271 adult 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.

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 3 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 3. Adverse Reactions Identified in Two Placebo-Controlled Studies

Adverse Reaction	Nplate (n = 84)	Placebo (n = 41)
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 291 adult 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.

Bone Marrow Reticulin Formation and Collagen Fibrosis

Nplate administration may increase the risk for development or progression of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation of Nplate. In a clinical trial, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy.

An open-label clinical trial prospectively evaluated changes in bone marrow reticulin formation and collagen fibrosis in adult patients with ITP treated with Nplate or a non-US approved romiplostim product. Patients were administered romiplostim by SC injection once weekly for up to 3 years. Based on cohort assignment at time of study enrolment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1), year 2 (cohort 2), or year 3 (cohort 3) in comparison to the baseline bone marrow at start of the trial. Patients were evaluated for bone marrow reticulin formation and collagen fibrosis using the modified Bauermeister grading scale. From the total of 169 patients enrolled in the 3 cohorts, 132 (78%) patients were evaluable for bone marrow collagen fibrosis and 131 (78%) patients were evaluable for bone marrow reticulin formation. Two percent (2/132) of patients (both from cohort 3) developed Grade 4 findings (presence of collagen). There was no detectable bone marrow collagen in one patient on repeat testing 12 weeks after discontinuation of romiplostim. Progression of bone marrow reticulin formation (increase greater than or equal to 2 grades or more) or an increase to Grade 4 (presence of collagen) was reported in 7% (9/131) of patients.

Pediatric Patients

The data described below reflect median exposure to Nplate of 168 days for 59 pediatric patients (aged 1 to 17 years) with ITP for at least 6 months, of whom 47.5% were female, across the randomized phase of two placebo-controlled trials. Table 4 presents the most common adverse reactions experienced by at least 5% of the pediatric patients (1 year and older) receiving Nplate across the two placebo-controlled trials with at least a 5% higher incidence in patients who received Nplate compared to those who received placebo.

Table 4. Common Adverse Reactions (≥ 5% Incidence and ≥ 5% More Frequent on the Nplate Arm) from Two Placebo-Controlled Trials in Pediatric Patients with ITP for at least 6 months

Adverse Reactions^a by Body System	Nplate (%) (N=59)	Placebo (%) (N=24)
<u>Infections and Infestations</u>		
Upper Respiratory Tract Infection	18 (31%)	6 (25%)
Ear infection	3 (5%)	0
Gastroenteritis	3 (5%)	0
Sinusitis	3 (5%)	0
<u>Respiratory, Thoracic and Mediastinal Disorders</u>		
Oropharyngeal Pain	15 (25%)	1 (4%)
<u>Gastrointestinal Disorders</u>		
Diarrhea	12 (20%)	3 (13%)
Abdominal Pain Upper	8 (14%)	1 (4%)
<u>Skin and Subcutaneous Tissue Disorders</u>		
Rash	9 (15%)	2 (8%)
Purpura	4 (7%)	0
Urticaria	3 (5%)	0
<u>General Disorders and Administration Site Conditions</u>		
Pyrexia	14 (24%)	2 (8%)
Peripheral Swelling	4 (7%)	0
<u>Injury, Poisoning and Procedural Complications</u>		
Contusion	24 (41%)	8 (33%)

^aMedDRA version 20.1 is used.

In pediatric patients of age ≥ 1 year receiving Nplate for ITP, adverse reactions with an incidence of $\geq 25\%$ in the two randomized trials were: contusion (41%), upper respiratory tract infection (31%), and oropharyngeal pain (25%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Nplate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Erythromelalgia
- Hypersensitivity
- Angioedema

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Nplate in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. 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 in adult patients with ITP, the incidence of pre-existing antibodies to romiplostim was 5% (53/1112) and the incidence of binding antibody development during treatment with Nplate or a non-US approved romiplostim product was 4% (50/1112). The incidence of pre-existing antibodies to endogenous TPO was 4% (40/1112) and the incidence of binding antibody development to endogenous TPO during treatment was 3% (38/1112). Of the patients with positive binding antibodies that developed to romiplostim or to TPO, five patients had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No apparent correlation was observed between antibody activity and clinical effectiveness or safety.

In pediatric studies, the incidence of binding antibodies to Nplate at any time was 7.8% (22/282). Of the 22 patients, 2 patients had pre-existing binding non-neutralizing Nplate antibodies at baseline. Additionally, 2.5% (7/282) developed neutralizing antibodies to Nplate. A total of 3.2% (9/282) patients had binding antibodies to TPO at any time during Nplate treatment. Of these 9 patients, 2 patients had pre-existing binding non-neutralizing antibodies to TPO. All patients were negative for neutralizing activity to TPO.

A post marketing registry study involving patients with thrombocytopenia on Nplate or a non-US approved romiplostim product was conducted to assess the long-term consequences of the anti-romiplostim antibodies. Patients who lacked response or lost response to Nplate or a non-US approved romiplostim product were enrolled. The incidence of new binding antibody development was 3% (5/186) to romiplostim and 1% (2/186) to TPO. One patient was positive for binding antibodies to both romiplostim and TPO. Of the five patients with positive binding antibodies to romiplostim, two (1%) were positive for neutralizing antibodies to romiplostim only.

Nineteen confirmed pediatric patients were included in the post marketing registry study. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralizing antibodies to romiplostim. There were no antibodies detected to TPO.

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

Nplate may be used with other medical ITP therapies, such as corticosteroids, danazol, azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin [see *Clinical Studies (14.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, Nplate may cause fetal harm when administered to a pregnant woman (see *Data*). Limited available data with Nplate use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. 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 (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In rat and rabbit embryo-fetal development toxicity studies, no evidence of fetal harm was observed at romiplostim doses up to 11 times (rats) and 82 times (rabbits) the maximum human dose (MHD) based on systemic exposure (AUC). 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.

Women who become pregnant during Nplate treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

8.2 Lactation

Risk Summary

There is no information regarding the presence of romiplostim in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Due to the potential for serious adverse reactions in a breastfed child from Nplate, advise women not to breastfeed during treatment with Nplate.

8.4 Pediatric Use

Safety and effectiveness have been established in pediatric patients age 1 year and older with ITP for at least 6 months evaluated in two randomized, placebo-controlled studies [see *Adverse Reactions (6.1)*, *Clinical Studies (14.2)*]. The pharmacokinetics of romiplostim have been evaluated in pediatric patients 1 year and older with ITP [see *Clinical Pharmacology (12.3)*]. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older. The safety and efficacy of Nplate in pediatric patients younger than 1 year with ITP have not been established. Serum concentrations of romiplostim in pediatric patients with ITP were within the range observed in adult patients with ITP receiving the same dose range of romiplostim.

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.

10 OVERDOSAGE

Overdoses due to medication errors have been reported in patients receiving Nplate. 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 (2.1, 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 (romiplostim) for injection 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. Each single-dose 250 mcg vial of Nplate contains the following: 375 mcg romiplostim, 1.2 mg L-histidine, 30 mg mannitol, 0.03 mg polysorbate 20, 15 mg sucrose, and sufficient HCl to adjust the pH to a target of 5.0. Each single-dose 500 mcg vial of Nplate contains the following: 625 mcg romiplostim, 1.9 mg L-histidine, 50 mg mannitol, 0.05 mg polysorbate 20, 25 mg sucrose, 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 adult 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.

Serum concentrations of romiplostim in pediatrics with ITP were within the range observed in adult ITP patients receiving the same dose range of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in pediatric patients with ITP.

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 Adults with Chronic ITP

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

Studies 1 (NCT00102336) and 2 (NCT00102323)

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 (i.e., 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 5. 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 5. Results from Placebo-Controlled Studies^a

Outcomes	Study 1		Study 2	
	Nonsplenectomized Patients		Splenuctomized Patients	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
Platelet Responses and Rescue Therapy				
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 ≥ 50 × 10 ⁹ /L, average	15	1	12	0
Requiring Rescue Therapy, n (%)	8 (20%)	13 (62%)	11 (26%)	12 (57%)
Reduction/Discontinuation of Baseline Concurrent ITP Medical Therapy				
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 (%) ^b	4/11 (36%)	3/10 (30%)	8/12 (67%)	0/6 (0%)

^a All *p* values < 0.05 for platelet response and rescue therapy comparisons between Nplate and placebo.

^b 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.

Study 3 (NCT00116688) Extension Study

Patients who had participated in either Study 1 or Study 2 were withdrawn from study medications. If platelet counts subsequently decreased to ≤ 50 × 10⁹/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 ≥ 50 × 10⁹/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 × 10⁹/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.

14.2 Pediatric Patients with ITP

The safety and efficacy of Nplate in pediatric patients 1 year and older with ITP for at least 6 months were assessed in two double-blind, placebo-controlled clinical trials.

Study 4 (NCT01444417)

In Study 4, patients refractory or relapsed after at least one prior ITP therapy with a platelet count ≤ 30 × 10⁹/L were stratified by age and randomized (2:1) to receive Nplate (n=42) or placebo (n=20). The starting dose for all ages was 1 ug/kg weekly. Over a 24-week treatment period, dose was titrated up to a maximum of 10 µg/kg weekly of either Nplate or placebo in an effort to maintain a target platelet count of ≥ 50 × 10⁹/L to 200 × 10⁹/L.

The median age of the patients was 9.5 years (range 3 to 17) and 57% were female. Approximately 58% of patients had a baseline count ≤ 20 × 10⁹/L, which was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly immunoglobulins and corticosteroids) was 81% in the group treated with Nplate and 70% in the group treated with placebo. One patient in each group had undergone splenectomy.

Study 4 results are shown in Table 6. The efficacy of Nplate in this trial was measured by the proportion of patients receiving Nplate achieving a durable platelet response and the proportion of patient achieving an overall platelet response. A durable platelet response was defined as achieving at least 6 weekly platelet counts $\geq 50 \times 10^9/L$ during weeks 18 through 25 of treatment. A transient platelet response was defined as a weekly platelet count $\geq 50 \times 10^9/L$ for 4 or more times during weeks 2 through 25, but without durable platelet response. An overall platelet response was defined as a durable or a transient platelet response. Platelet responses were excluded for 4 weeks after receiving rescue medications.

Table 6. Results from Pediatric Placebo-Controlled Studies^a

Outcomes	Study 4	
	Nplate (n = 42)	Placebo (n = 20)
Platelet Responses and Rescue Therapy		
Durable Platelet Response ^a , n (%)	22 (52%)	2 (10%)
Overall Platelet Response ^a , n (%)	30 (71%)	4 (20%)
Number of Weeks With Platelet Counts $\geq 50 \times 10^9/L$, median ^a	12	1

^a All *p* values < 0.05 for platelet response between Nplate and placebo.

Study 5 (NCT00515203)

In study 5, patients diagnosed with ITP at least 6 months prior to enrollment with a platelet count $\leq 30 \times 10^9/L$ were stratified by age and randomized (3:1) to receive Nplate (n=17) or placebo (n=5). The starting dose for all ages was 1 ug/kg weekly. Over a 12-week treatment period dose was titrated up to a maximum of 10 $\mu\text{g}/\text{kg}$ weekly of either Nplate or placebo in an effort to maintain a target platelet count of $\geq 50 \times 10^9/L$ to $250 \times 10^9/L$.

The median age of the patients was 10 years (range 1 to 17 years) and 27.3% of patients were female. Approximately 82% of patients had a baseline count $\leq 20 \times 10^9/L$, which was similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies (predominantly IVIG and corticosteroids) was 88% in the group treated with Nplate and 100% in the group treated with placebo. Six patients in the Nplate group and 2 patients in the placebo group had undergone splenectomy.

The efficacy of Nplate in this trial was measured by the proportion of patients who achieved a platelet count of $\geq 50 \times 10^9/L$ for 2 consecutive weeks and by the proportion of patients who achieved an increase in platelet count of $\geq 20 \times 10^9/L$ above baseline for 2 consecutive weeks. Platelet responses within 4 weeks following rescue medications use were excluded. Of the 17 patients who received romiplostim, 15 achieved a platelet count of $\geq 50 \times 10^9/L$ for 2 consecutive weeks (88.2%, 95% CI: 63.6%, 98.5%).

The same 15 patients also achieved an increase in platelet count of $\geq 20 \times 10^9/L$ above baseline for 2 consecutive weeks during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). None of the patients treated with placebo achieved either endpoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

Nplate (romiplostim) for injection is supplied as a sterile, preservative-free, solid white lyophilized powder in single-dose vials that deliver 250 mcg (NDC 55513-221-01) and 500 mcg (NDC 55513-222-01) of romiplostim.

Store Nplate vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

If needed, unopened Nplate vials may be stored in the original carton at room temperature up to a maximum of 25°C (77°F) for a single period of up to 30 days. The new expiration date must be written in the space provided on the

carton. Once stored at room temperature, do not place back in the refrigerator. If not used within the 30 days, discard Nplate.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following risks and considerations for Nplate:

- 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 may increase the risk of reticulin fiber formation within the bone marrow. This formation may improve upon discontinuation. 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 increases the risk of progression to acute myelogenous leukemia in patients with myelodysplastic syndromes.
- Platelet counts and CBCs must be performed weekly until a stable Nplate dose has been achieved; thereafter, platelet counts and CBCs 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.

Pregnancy:

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation:

- Advise women not to breastfeed during treatment with Nplate [*see Use in Specific Populations (8.2)*].

AMGEN[®]

Nplate[®] (romiplostim)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License No. 1080

Patent: <http://pat.amgen.com/nplate/>

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www.nplate.com

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MEDICATION GUIDE

Nplate® (N-plät)
(romiplostim)
for injection

What is the most important information I should know about Nplate?

Nplate can cause serious side effects, including:

- **Worsening of a precancerous blood condition to a blood cancer (leukemia).** Nplate is not for use in people with a precancerous condition called myelodysplastic syndromes (MDS), or for any condition other than chronic (lasting a long time) immune thrombocytopenia (ITP). If you have MDS and receive Nplate, your MDS condition may worsen and become an acute leukemia. If MDS worsens to become acute leukemia you may die sooner from the acute leukemia.
- **Higher risk for blood clots.**
 - You may have a higher risk of getting a blood clot if your platelet count becomes high during treatment with Nplate. You may have severe complications or die from some forms of blood clots, such as clots that spread to the lungs or that cause heart attacks or strokes.
 - If you have a chronic liver disease, you may get blood clots in the veins of your liver. This may affect your liver function.

Your healthcare provider will closely monitor your Nplate dose and blood tests, including platelet counts during treatment.

- Injection of too much Nplate may cause a dangerous increase in your blood platelet count and serious side effects.
- Your healthcare provider may change your dose or stop Nplate, depending upon the change in your blood platelet count. You must have blood platelet counts done before you start, during, and after Nplate therapy is stopped.

See “What are the possible side effects of Nplate?” for other side effects of Nplate.

What is Nplate?

Nplate is a prescription medicine used to treat low blood platelet counts (thrombocytopenia) in:

- adults with chronic immune thrombocytopenia (ITP) when certain medicines or surgery to remove your spleen have not worked well enough.
- children 1 year of age and older with ITP for at least 6 months when certain medicines or surgery to remove your spleen, have not worked well enough.
- Nplate is not for use in people with a precancerous condition called myelodysplastic syndrome (MDS), or low platelet count caused by any condition other than chronic (lasting a long time) immune thrombocytopenia (ITP).
- Nplate is only used if your low platelet count and medical condition increase your risk of bleeding.
- Nplate is used to try to keep your platelet count about 50,000 per microliter in order to lower the risk for bleeding. Nplate is not used to make your platelet count normal.
- It is not known if Nplate is safe and effective in children under the age of 1.

Before receiving Nplate, tell your healthcare provider about all of your medical conditions, including if you:

- have had surgery to remove your spleen (splenectomy)
- have a bone marrow problem, including a blood cancer or MDS
- have or had a blood clot
- have chronic liver disease
- have bleeding problems
- are pregnant or plan to become pregnant. Nplate may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with Nplate.

Pregnancy Surveillance Program: Women who become pregnant during Nplate treatment are encouraged to enroll in Amgen’s Pregnancy Surveillance Program. The purpose of this program is to collect safety information about the health of you and your baby. Contact the program as soon as you become aware of the pregnancy, or ask your healthcare provider to contact the program for you. You or your healthcare provider can get information and enroll in the program by calling 1-800-77-AMGEN (1-800-772-6436).

- are breastfeeding or plan to breastfeed. Nplate may pass into your breast milk and harm your baby. **Do not** breastfeed during treatment with Nplate and for 2 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal products. Know the medicines you take. Keep a list of them and show it to your healthcare provider or pharmacist when you get a new medicine.

How will I receive Nplate?

Before you receive Nplate you should first talk with your healthcare provider and understand the benefits and risks of Nplate.

- Nplate is given under the skin (subcutaneous injection) one time each week by your healthcare provider.

- Your healthcare provider will check your platelet count every week and change your dose of Nplate as needed. This will continue until your healthcare provider decides that your dose of Nplate can stay the same. After that, you will need to get blood tests every month. When you stop receiving Nplate, you will need blood tests for at least 2 weeks to check if your platelet count drops too low.
- Tell your healthcare provider about any bruising or bleeding that occurs during treatment with Nplate.
- If you miss a scheduled dose of Nplate, call your healthcare provider to schedule your next dose as soon as possible.

What should I avoid while receiving Nplate?

Avoid situations that may increase your risk of bleeding, such as missing a scheduled dose of Nplate. You should schedule your next dose as soon as possible and call your healthcare provider.

What are the possible side effects of Nplate?

Nplate may cause serious side effects. See “What is the most important information I should know about Nplate?”

The most common side effects of NPLATE in adults include:

- headache
- joint pain
- dizziness
- trouble sleeping
- muscle tenderness or weakness
- pain in the arms and legs
- stomach (abdomen) pain
- shoulder pain
- indigestion
- tingling or numbness in hands and feet

The most common side effects of Nplate in children 1 year of age and older include:

- inflammation of the passages in the nose and throat (nasopharyngitis)
- upper respiratory tract infection
- itchy, runny, or blocked nose (rhinitis)
- sore throat and discomfort with swallowing (pharyngitis)
- inflammation of the eye (conjunctivitis)
- ear infection
- inflammation in the lining of the intestines (gastroenteritis)
- inflammation of the sinuses (sinusitis)
- cough
- pain in mouth and throat (oropharyngeal pain)
- upper stomach (abdomen) pain
- diarrhea
- rash
- bleeding beneath the surface of the skin or bruising under the skin (purpura)
- itchy rash (urticaria)
- fever (pyrexia)
- swelling in the limbs/hands/feet (peripheral swelling)
- bruising (contusion)

People who take Nplate may have an increased risk of developing new or worsening changes in the bone marrow called “increased reticulins.” These changes may improve if you stop taking Nplate. Your healthcare provider may need to check your bone marrow for this problem during treatment with Nplate.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Amgen at 1-800-77-AMGEN (1-800-772-6436).

General information about the safe and effective use of Nplate.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about Nplate that is written for health professionals.

What are the ingredients in Nplate?

Active ingredient: romiplostim

Inactive ingredients: L-histidine, mannitol, polysorbate 20, sucrose, and hydrochloric acid

Nplate® (romiplostim)

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799

US License No. 1080.

Patent: <http://pat.amgen.com/nplate/>

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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