BLA 125268 Nplate (romiplostim)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Nplate (romiplostim)
- To establish the long-term safety and safe use of Nplate (romiplostim) through periodic monitoring of all patients who receive Nplate (romiplostim) for changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and medication errors associated with serious outcomes.

II. REMS ELEMENTS

A. Medication Guide

The Medication Guide will be delivered by the Regional Medical Liaisons (RMLs) and sales representatives prior to program enrollment, made available through the Nplate.com website, and included in each Nplate vial package. A Medication Guide will be dispensed with each Nplate dose. Each healthcare provider will provide each patient with the Nplate Medication Guide prior to each dose. Please see the appended Medication Guide.

B. Communication Plan

Amgen will implement a communication plan to healthcare providers to support implementation of the REMS.

Educational materials and the Medication Guide will be distributed to HCPs prior to ordering Nplate.

Nplate NEXUS Program Website

- The Nplate™ NEXUS Program website will be included as a link on the Nplate.com website. This site will contain information about the Nplate™ NEXUS Program as well as PDF versions of program forms and tools. The tabbed components on the Nplate™ NEXUS Program website will reflect the REMS goals and the primary content of the Nplate™ NEXUS Program Brochure. Additionally, all program forms will be available under the resource tab.

Healthcare Provider Awareness

- **Nplate™ NEXUS Program Healthcare Provider Introductory Letter**

  The Nplate™ NEXUS Program Healthcare Provider Introductory Letter will be distributed to healthcare providers via the Nplate™ NEXUS website at product launch along with other Nplate™ NEXUS Program educational materials. The letter will state that Nplate is only available through the Nplate™ NEXUS Program. HCPs must be enrolled in the program to prescribe Nplate and patients must be enrolled in the program to receive Nplate. Additionally, the letter will provide a description of the program created to establish the long-term safety and safe use of Nplate and the prescribers role. Finally, the letter will include direction on how to enroll in the Nplate™ NEXUS Program. Please see appended Nplate™ NEXUS Program Healthcare Provider Introductory Letter.

C. Elements to Assure Safe Use

1. Nplate will only be prescribed by healthcare providers who are specially certified.

Certification of prescribers into the Nplate™ NEXUS Program requires prescribers to enroll in the Nplate™ NEXUS Program and attest to the following:

- I have read the full prescribing information for Nplate
- I understand that Nplate is only approved 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.
- I understand that Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- I understand that Nplate should not be used in an attempt to normalize platelet counts.
- I understand that Nplate is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
- I understand the following risks are associated with Nplate:
  - Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Clinical studies have not excluded a risk of progression to bone marrow fibrosis with cytopenias. If the patient develops new or worsening morphological abnormalities or cytopenia(s), I should discontinue treatment with Nplate and consider a bone marrow biopsy, including staining for fibrosis.
  - Discontinuation of Nplate may result in thrombocytopenia of greater severity than was present prior to Nplate therapy. This worsened thrombocytopenia resolved within 14 days in the clinical trials.
  - 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 this risk.

  - Nplate may increase the risk for hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS)

- I understand that each patient should be monitored as follows to assure safe use of Nplate:
  - Examine the peripheral smear closely to establish a baseline level of cellular morphologic abnormalities.
  - Monitor CBCs, including platelet counts and peripheral blood smears weekly until a stable Nplate dose has been achieved. Thereafter, CBCs, including platelet counts and peripheral blood smears, should be monitored at least monthly.
  - If Nplate is discontinued, I will obtain weekly CBCs, including platelet counts for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to treatment guidelines.
- I understand how to properly dose and administer Nplate in order to prevent medication errors.
- I understand that I must complete this Nplate™ NEXUS Program Healthcare Provider Enrollment Form to enroll myself in the Nplate™ NEXUS Program (I only need to enroll once).
- I will enroll each patient by assisting in the completion of the Nplate™ NEXUS Program Patient Enrollment Form and completing the Nplate™ NEXUS Program Patient Baseline Data Form. I will complete the Nplate™ NEXUS Program Patient Baseline Data Form at the time of enrollment or within 30 days of patient enrollment. I understand that baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of Nplate.
- I will provide each patient with the Nplate™ Medication Guide prior to each dose, and counsel each patient on the risks and benefits of Nplate™.
- I will complete the Nplate™ NEXUS Program Patient Enrollment Form for each patient; (1) obtain patient signature acknowledging receipt of Nplate™ Medication Guide, (2) obtain patient's signature authorizing disclosure of health information related to the Nplate™ NEXUS Program, and (3) send the completed Nplate™ NEXUS Program Patient Enrollment Form to the Nplate™ NEXUS Program for patient enrollment.
- I will counsel each patient to carry a Patient ID Card and Dosing Tracker that identifies the risks with Nplate and contains the Nplate™ NEXUS Program access number.
- I will evaluate the safe-use and patient status every 6 months to determine whether the patient should continue Nplate and if so, authorize treatment for another 6 months.
- I will notify the Nplate™ NEXUS Program when a patient discontinues Nplate by completing the Nplate™ NEXUS Program Patient Discontinuation/Post-

Discontinuation Follow-Up Form at the time of Nplate™ discontinuation and 6 months later.

- I will promptly report to the Nplate™ NEXUS Program any adverse events occurring in the course of the use of the drug as described in the Nplate™ NEXUS Program Safety Questionnaire.
- I understand that Amgen will be regularly evaluating compliance with the Nplate™ NEXUS Program, and that Amgen reserves the right to restrict my ability to enroll future patients or take other appropriate measures at any time if I fail to comply with Nplate™ NEXUS Program requirements.

I further understand that I have sole responsibility for all medical judgments and treatments, and have sole responsibility to, prior to Nplate administration, counsel each patient on the risks of Nplate, and provide each patient with all necessary warnings concerning Nplate.

The Nplate™ NEXUS Program Healthcare Provider Enrollment Form can be completed and faxed.

Please see the following appended documents:

- Nplate™ NEXUS Program Healthcare Provider Enrollment Form
- Nplate™ NEXUS Program Brochure
- Nplate™ NEXUS Program Training Kit Folder
- Nplate™ Dose Calculator
- Nplate™ NEXUS Program Website
- Nplate™ NEXUS Program Call Center

2. **Nplate will only be dispensed by practitioners (physicians' offices) and healthcare settings (i.e., hospitals/institutions) that are specially certified:**

   a. Only certified prescribers (as described above) who are enrolled in the Nplate™ NEXUS Program will be able to dispense and administer Nplate. Nplate will be distributed to enrolled certified prescribers via a drop-ship program through which Amgen maintains direct control over who purchases Nplate. The enrolled certified prescriber may order Nplate through their usual distributor and the distributor will transmit the order to the Nplate™ NEXUS Program. Please see appended Procedure for Prescriber Distribution (HCPs/Hospital/Institution).

   b. Only practitioners (physicians' offices) and healthcare settings (i.e., hospitals/institutions) enrolled in the Nplate™ NEXUS Program will be able to dispense and/or administer Nplate. In addition to the enrollment of a designated person at a hospital, each healthcare provider who prescribes Nplate™ needs to be enrolled in the Nplate™ NEXUS Program. Enrollment requires the hospitals /institutions to:

- Complete the Nplate™ NEXUS Program Institution Enrollment Form;
- Develop a system, order sets, protocols, or other measures to ensure that Nplate is only dispensed to inpatients and outpatients (e.g., in a clinic) after verifying that the prescribing healthcare provider and patient are enrolled in the Nplate™ NEXUS Program;
- Train and provide educational materials to appropriate staff responsible for prescribing, dispensing, and administering Nplate regarding the safe and appropriate use of Nplate, program monitoring requirements (including dispensing a Medication Guide with each dose), program adverse event reporting requirements, and institution documentation requirements;
- To develop a system to ensure patients started on Nplate as an inpatient are transitioned to an outpatient healthcare provider that is enrolled (or will be enrolled) in the Nplate™ NEXUS Program; and
- To develop a process and system to track Nplate™ NEXUS Program compliance and cooperate with periodic audits to assure that Nplate is used in accordance with the program requirements.

  Product tracking includes the following information:

  - Name and unique identification number of the enrolled prescribing healthcare provider
  - Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate
  - Date of each Nplate order (including number of vials ordered and vial sizes)
  - Number of Nplate vials, vial sizes and date of each dose given to each patient
  - Overall inventory for the set period of time including the total number of vials ordered (including vial sizes), dispensed, and in stock.

Nplate will only be distributed to enrolled hospitals/institutions via a drop-ship program through which Amgen maintains direct control over who purchases Nplate. The enrolled institution may order Nplate through their usual distributor; the distributor will transmit the order to the Nplate™ NEXUS Program. Please see appended Procedure for Prescriber Distribution (HCPs/Hospital/Institution).

The Nplate™ NEXUS Program Institution Enrollment Form can be completed and faxed. Please see appended Nplate™ NEXUS Program Institution Enrollment Form and Procedures for Direct Shipment to Registered Healthcare Providers and Hospitals/Institutions.

3. Each patient treated with Nplate must be enrolled in the Nplate™ NEXUS Program for documentation of safe use conditions.

Patient enrollment requires the patient to attest to the following:

- Read and understand the Medication Guide for Nplate that my prescriber has given to me.
- Ask and discuss any questions or concerns about Nplate or my treatment with my health care provider.
- Be aware that Nplate is associated with the following risks:
    - Long-term use of Nplate may cause changes in my bone marrow. These changes may lead to abnormal blood cells or my body making less blood cells.
    - When I stop receiving Nplate, my low blood platelet count (thrombocytopenia) may become worse than before I started receiving Nplate.
    - I have a higher chance of getting a blood clot if my platelet count is too high during treatment with Nplate.
    - Nplate may worsen blood cancers. Nplate is not for use in patients with blood cancer or a precancerous condition called mylodysplastic syndrome (MDS).
- Report any adverse events to my prescriber.
- Understand that I should not discontinue Nplate without talking to my health care provider.
- Understand that, if I receive Nplate in the hospital, that upon discharge, I should immediately follow up with a healthcare provider to determine if continued Nplate treatment is appropriate.
- Understand that I should always carry my Patient ID Card and Dosing Tracker.
- Notify the Nplate™ NEXUS Program if I switch to a different healthcare provider for Nplate treatment by calling 1-877-NPLATE1 (1-877-675-2831).
- Understand that in order to receive Nplate, I will be automatically enrolled in the Nplate™ NEXUS Program. My healthcare provider will monitor how I am doing on Nplate and report to the Nplate™ NEXUS Program every 6 months about certain serious side effects, and to make sure Nplate continues to be right for me.
- Understand that if I do not sign this Patient Acknowledgement, I will not be enrolled in the Nplate™ NEXUS Program and will not be able to receive Nplate.

The Nplate™ NEXUS Program Patient Enrollment Form can be completed and faxed to the Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830).

Please see the following appended documents:

- Nplate™ NEXUS Program Patient Enrollment Form
- Patient/Caregiver Program Introductory Letter
- What is Nplate™ NEXUS Program? – a brochure for Nplate patients and caregivers
- Patient ID Card and Dosing Tracker

4. Each patient treated with Nplate is subject to certain monitoring.

a. Safety Monitoring - Prescribers must complete a Nplate™ NEXUS Program Patient Baseline Data Form for each patient within 30 days of enrollment and a Nplate™ NEXUS Program Safety Questionnaire every six months during treatment with Nplate. The Nplate™ NEXUS Program Safety Questionnaire also requires the prescriber to authorize continued treatment with Nplate. The Nplate™ NEXUS Program Call Center will remind the Nplate prescriber when it is time to complete the questionnaires for each patient. All reported serious adverse events will be further investigated and followed by Amgen Global Safety. These forms and questionnaires can be completed and faxed to Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830), or completed over the telephone. Please see appended Nplate™ NEXUS Patient Safety Registry.

b. Patient Discontinuation - At the time the prescriber determines that a patient should be discontinued from Nplate, the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form must be completed at the time of discontinuation and 6 months later.

Please see the following appended documents:

- Nplate™ NEXUS Program Patient Baseline Data Form
- Nplate™ NEXUS Program Safety Questionnaire
- Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form
- Risk-Specific Adverse Event Report Forms
    - Nplate™ NEXUS Program Thrombotic/Thromboembolic Complications
    - Nplate™ NEXUS Program Hematological Malignacy/MDS
    - Nplate™ NEXUS Program Medication Errors Associated with Serious Outcomes.
    - Nplate™ NEXUS Program Bone Marrow Reticulin/Bone Marrow Fibrosis
    - Nplate™ NEXUS Program Worsened Thrombocytopenia After Cessation of Nplate

D. Implementation System

The Implementation System includes the following:

- Nplate™ NEXUS Program Call Center will maintain a database of all enrolled certified healthcare settings and practitioners that dispense and/or administer the drug, and patients who have documentation of safe-use conditions to monitor and evaluate implementation of elements
- Nplate™ NEXUS Program Call Center will monitor distribution of Nplate to determine whether the drug is only drop-shipped to certified hospitals and prescribers who dispense the drug.
- Nplate™ NEXUS Program Call Center will monitor certified healthcare settings and practitioners ordering to ensure only enrolled patients are receiving Nplate.
- Nplate™ NEXUS Program Call Center will monitor healthcare setting and practitioner compliance with the baseline data collection, the periodic safety monitoring and reauthorization, discontinuation procedure, and post-discontinuation follow-up of all patients treated with Nplate. If a healthcare setting or practitioner is found to be non-compliant with the Nplate™ NEXUS Program, Amgen may prevent the healthcare setting or practitioner from enrolling new patients and require the prescriber to order Nplate directly through the Nplate™ NEXUS Program.
- Based on monitoring and evaluation of these elements to assure safe-use, Amgen will take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

REMS Assessments (see III below for content) will be submitted to FDA every 6 months for the first 24 months following approval, then annually (from REMS approval date) thereafter.

III. INFORMATION NEEDED FOR ASSESSMENTS

REMS Assessments will include the following information:

- An assessment of enrollment and discontinuation statistics for patients, prescribers, and institutions
    - The number of patients enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
    - The number of patient person-years for enrolled patients in the Nplate™ NEXUS Program.
    - The number of new patients enrolled during the reporting period.
    - The number of patients who received Nplate who were not enrolled (during the reporting period and cumulative).
    - The number of patients who discontinued Nplate (during the reporting period and cumulative).

  - The number of patients who were lost-to-follow-up (during the reporting period and cumulative).
  - The number of patients who discontinue Nplate and are re-enrolled for another course of Nplate treatment (during the reporting period and cumulative).
  - The number of healthcare providers enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
  - The number of new healthcare providers enrolled in the Nplate™ NEXUS Program during the reporting period.
  - The number of enrolled healthcare providers actively prescribing Nplate during the reporting period.
  - The number of healthcare providers who have ordered/prescribed Nplate who were not enrolled (during the reporting period and cumulative).
  - The number of institutions enrolled in the Nplate™ NEXUS Program (during the reporting period and cumulative).
  - The number of institutions who treated a patient with Nplate during the reporting period.
  - The number of institutions who ordered/prescribed/dispensed Nplate that were not enrolled (during the reporting period and cumulative).
- A narrative summary will be written by Amgen Global Safety with analysis of patients who discontinued Nplate treatment including duration of treatment and the reason for discontinuation during the reporting period.
- The total number of safety stock orders requested, filled, and denied for prescribers during the reporting period.
  - A summary and analysis of safety stock orders per prescriber during the reporting period.
- The total number of safety stock orders requested, filled, and denied for institutions during the reporting period.
  - A summary and analysis of safety stock orders per institution during the reporting period.
- A narrative summary with analysis of reports with inpatient to outpatient (or vice versa) transition issues.
- An assessment of use data establishing the circumstances of the use of Nplate
  - The extent of use in the indicated population
  - The extent of use in patients by various baseline data parameters (e.g., platelet count, spleen status, number of previous therapies, duration of ITP, previous treatment with Nplate, age)
  - The extent of use for treatment of thrombocytopenia associated with chemotherapy or MDS

  - The extent of use for treatment for other reasons
  - The extent of use in inpatients
  - The extent of use in outpatients affiliated with a hospital/institution (e.g., clinics)
  - The extent of use in outpatients not affiliated with a hospital/institution (e.g., doctor's office)

- An assessment of prescriber compliance with elements of certification: completing the Nplate™ NEXUS Program Patient Baseline Data Form, Nplate™ NEXUS Program Safety Questionnaire with reauthorization, and the Discontinuation/Post-Discontinuation Follow-Up Form for each patient during the reporting period and cumulative.
- The number of prescribers not complying with certification requirements who must order Nplate directly from the Nplate™ NEXUS Program (no longer allowed to order through a distributor) during the reporting period and cumulative. Describe the types of non-compliance.
- The number and summary of prescribers who were un-enrolled from the Nplate™ NEXUS Program during the reporting period and cumulative.
- The number of non-compliant institutions that must order Nplate directly from the Nplate™ NEXUS Program (no longer allowed to order through a distributor) during the reporting period and cumulative. Describe the types of non-compliance.
- A summary of the institution audits performed during the reporting period. This may include but not be limited to the number of institutions audited, describing the institution compliance with prescriber enrollment, patient enrollment, Baseline Data Form completion, and maintaining Nplate product tracking information. This summary should identify any deviations and the corrective actions taken. Please see the appended Monitoring and Compliance of Nplate™ NEXUS Program Elements.
- Amgen Global Safety will write a narrative summary and analysis of the following adverse events reported during the reporting period including:
  - Bone marrow reticulin formation
  - Bone marrow fibrosis
  - Newly diagnosed hematological malignancies or MDS
  - Progression of previously diagnosed hematological malignancies or precancerous conditions (e.g., MDS)
  - Worsening thrombocytopenia upon cessation of Nplate
  - Thrombotic/Thromboembolic events
  - Medication errors resulting in a serious outcome
  - Death
- The total number and percentage of patients who received a bone marrow biopsy due to a change in the patient's peripheral smear (cumulative).

- The total number and percentage of patients who had a diagnosis of bone marrow fibrosis (cumulative).
- The total number and percentage of patients who had a diagnosis of a new hematological malignancy (cumulative).
- The total number and percentage of patients who had progression of a previously diagnosed hematological malignancy (cumulative).
- The total number and percentage of patients who had worsening thrombocytopenia upon cessation of Nplate (cumulative).
- The total number and percentage of patients who had a thrombotic/thromboembolic event (cumulative).
- The total number and percentage of patients who had a serious outcome as a result of a medication error (cumulative).
- Where clinical data are incomplete concerning events of interest (e.g., bone marrow fibrosis, hematological malignancy, thrombotic/thromboembolic complications, worsened thrombocytopenia upon cessation of Nplate, serious complications due to medication error, and death) or data points of interest, the report will include a complete description of Amgen's attempts to obtain the missing data. If necessary to establish the cause of death for a patient receiving Nplate, Amgen will obtain information from the National Death Index of the National Center for Health Statistics, Centers for Disease Control.
- A summary and analysis of unintended interruptions in treatment (e.g., interruptions due to shipment delays and other logistical issues). This summary should describe any corrective actions taken.
- A summary of all the changes to the Nplate™ NEXUS Program that were implemented during the reporting period.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- An assessment of healthcare provider and patient understanding regarding the safe-use of Nplate (i.e., the results of surveys administered to prescribers and patients). The survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to prescribers and patients in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of physicians to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

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 ≥ 50 x 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 x 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 (≥ 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)

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.

----------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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 ≥ 5 mcg/kg and six received doses ≥ 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

Preferred Term	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 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 x 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 (50×10^9/L to 200×10^9/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 19×10^9/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 14×10^9/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[a]

Outcomes	Study 1 Nonsplenectomized Patients		Study 2 Splenectomized 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 $\geq 50 \times 10^9$/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.

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 50×10^9/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.

www.Nplate.com

1-877-Nplate1 (1-877-675-2831)

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MEDICATION GUIDE

Nplate™ (N-plāt)

(romiplostim)

Read this Medication Guide before you start Nplate and before each Nplate injection. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Nplate can cause uncommon but serious side effects:

- **Bone marrow changes (increased reticulin and possible bone marrow fibrosis).** Long-term use of Nplate may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called "increased reticulin." It is not known if this may progress to a more severe form called "fibrosis." The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormalities in your blood tests. Your healthcare provider will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate.

- **Worsening low blood platelet count (thrombocytopenia) and risk of bleeding shortly after stopping Nplate.** When you stop receiving Nplate, your low blood platelet count (thrombocytopenia) may become worse than before you started receiving Nplate. These effects are most likely to happen shortly after stopping Nplate and may last about 2 weeks. The lower platelet counts during this time period may increase your risk of bleeding, especially if you are taking a blood thinner or other medicine that affects platelets. Your healthcare provider will check your blood platelet counts for at least two weeks after you stop taking Nplate. Call your healthcare provider right away to report any bruising or bleeding.

- **High platelet counts and higher chance for blood clots.** You have a higher chance of getting a blood clot if your platelet count is too 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. Your healthcare provider will check your blood platelet counts and change your dose or stop Nplate if your platelet counts get too high.

- **Worsening of blood cancers.** Nplate is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). If you have one of these conditions, Nplate may worsen your cancer or condition and may cause you to die sooner.

When you are being treated with Nplate, your healthcare provider will closely monitor your Nplate dose and blood tests, including platelet counts.

- Nplate is available only after you and your healthcare provider agree to join a program that is intended to help in the safe use of Nplate. This program is called the "Nplate NEXUS Program."

- Only a healthcare provider can inject a dose of Nplate. Injection of too much Nplate may cause a dangerous increase in your blood platelet count and serious side effects.

- During Nplate therapy, your healthcare provider may change your Nplate dose, depending upon the change in your blood platelet count. You must have blood platelet counts done before you start Nplate, during Nplate therapy, and after Nplate therapy is stopped.

- 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.

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

What is Nplate?

Nplate is a man-made protein medicine used to treat low blood platelet counts in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), when other medicine to treat your ITP is not the best choice for you or surgery to remove the spleen has not worked well enough.

Nplate is only:

- Prescribed by healthcare providers who are enrolled in the Nplate NEXUS Program.
- Given to patients who are enrolled in the Nplate NEXUS Program.
- Given by the enrolled healthcare provider or a provider under their direction. You may not give Nplate injections to yourself.

It is not known if Nplate works or if it is safe in people under the age of 18.

Nplate is for treatment of certain people with low blood platelet counts caused by chronic ITP, not low platelet counts caused by other conditions or diseases.

What should I tell my doctor before taking Nplate?

Tell your doctor about all 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 bleeding problems.
- Are pregnant, think you may be pregnant, or plan to get pregnant. It is not known if Nplate will harm an unborn baby.

  Pregnancy Registry: There is a registry for women who become pregnant during treatment with Nplate. If you become pregnant, consider this registry. The purpose of the registry is to collect safety information about the health of you and your baby. Contact the registry as soon as you become aware of the pregnancy, or ask your healthcare provider to contact the registry for you. You or your healthcare provider can get information and enroll in the registry by calling 1-877-Nplate1 (1-877-675-2831).

- Are breast-feeding or plan to breast-feed. It is not known if Nplate passes into your breast milk. You and your healthcare provider should decide whether you will take Nplate or breast-feed. You should not do both.

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

How should I take Nplate?

To receive Nplate, you must first talk with your healthcare provider and understand the benefits and risks of Nplate. You must agree to and follow all of the instructions in the Nplate NEXUS Program.

Before you can begin to receive Nplate, your healthcare provider will:

- Explain the Nplate NEXUS Program to you.
- Answer all of your questions about Nplate and the Nplate NEXUS Program.
- Make sure you read the Nplate Medication Guide.
- Have you sign the Nplate NEXUS Patient Enrollment Form.

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

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 have 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 while you are receiving Nplate.

If you miss a scheduled dose of Nplate, call your healthcare provider to arrange for 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 arrange for your next dose as soon as possible. Call your doctor or the Nplate NEXUS Program at 1-877-Nplate1 (1-877-675-2831).

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 are:

- Headache
- Joint pain
- Dizziness
- Trouble sleeping
- Muscle tenderness or weakness
- Pain in arms and legs
- Abdominal pain
- Shoulder pain
- Indigestion
- Tingling or numbness in hands and feet

These are not all the possible side effects of Nplate. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the Nplate NEXUS Program at 1-877-Nplate1 (1-877-675-2831) or FDA at 1-800-FDA-1088.

General information about the safe and effective use of Nplate.

This Medication Guide summarizes the most important information about Nplate. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Nplate that is written for health professionals.

What are the ingredients in Nplate?

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

Nplate™ (romiplostim)
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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www.Nplate.com
1-877-Nplate1 (1-877-675-2831)

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

Welcome, and thank you for your interest in Nplate™ (romiplostim).

Nplate™ is only available through the Nplate™ NEXUS (Network of EXperts Understanding and Supporting Nplate™ and patients) Program. This program is designed to promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Nplate™ for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The Nplate™ NEXUS Program consists of a patient registry and a requirement for prescribers to complete baseline and periodic safety information for every patient. As a prescriber, you must enroll in the Nplate™ NEXUS Program in order to prescribe Nplate™ by completing the Nplate™ NEXUS Program Healthcare Provider Enrollment Form.

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 attempt to normalize platelet counts.

The Nplate™ NEXUS Program includes a registry that enrolls all patients treated with Nplate™ in order to establish the long-term safety and safe use of Nplate™ through periodic monitoring. Specifically, the registry is focused on bone marrow reticulin formation and risk for bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate™, thrombotic/thromboembolic complications, and increased risk of of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS).

Before ordering Nplate™, you must enroll in the Nplate™ NEXUS Program. To get started, complete the enclosed Nplate™ NEXUS Program Healthcare Provider Enrollment Form and fax it to the Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830). In this kit, you will find resources that will help you understand the Nplate™ NEXUS Program, including:

– Nplate™ NEXUS Program Healthcare Provider Enrollment Form
– Nplate™ NEXUS Program Institution Enrollment Form
– Nplate™ NEXUS Program Brochure
– Nplate™ NEXUS Program Patient Enrollment Form
– Nplate™ NEXUS Program Patient Baseline Data Form
– Nplate™ NEXUS Program Safety Questionnaire
– Nplate™ NEXUS Program Patient Discontinuation/Post-discontinuation Follow-up Form
– Nplate™ Prescribing Information and Medication Guide
– Nplate™ Dose Calculator
– ITP Reimbursement Assistance Form
– MedWatch Form

Also in this kit is a complete set of materials for patients. You can order additional kits through your Amgen sales representative or by calling 1-877-NPLATE1 (1-877-675-2831). Each patient information kit includes:

– Nplate™ NEXUS Program Patient Program Enrollment Form
– Nplate™ NEXUS Program Patient Baseline Data Form
– "What is Nplate™ NEXUS?"—a brochure for Nplate™ patients and caregivers, including the Medication Guide
– Patient ID Card and Dosing Tracker

Nplate™ (romiplostim)
Nexus

For any questions about Nplate™ or the Nplate™ NEXUS Program, feel free to call a NEXUS Specialist at 1-877-NPLATE1 (1-877-675-2831) or online at www.nplate.com. You can also find more information at www.nplate.com, or ask your Nplate™ sales representative.

Important Safety Information

Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation. Additional risks include Bone Marrow Fibrosis, Thrombotic/Thromboembolic Complications, Lack or Loss of Response to Nplate™, and Hematologic Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS)..

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

We are happy to be of service to you and your patients.

Thanks,

The Nplate™ NEXUS team

Nplate™ (romiplostim) NEXUS Program Healthcare Provider Enrollment Form

I understand that Nplate™ (romiplostim) is only available through the Nplate™ NEXUS (Network of EXperts Understanding and Supporting Nplate™ and patients) Program and I agree to comply with the following program requirements:

- I have read the full Prescribing Information for Nplate™.
- I understand that Nplate™ is only approved 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.
- I understand that Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- I understand that Nplate™ should not be used in an attempt to normalize platelet counts.
- I understand that Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
- I understand the following risks are associated with Nplate™:
  - —Nplate™ administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Clinical studies have not excluded a risk of progression to bone marrow fibrosis with cytopenias. If the patient develops new or worsening morphological abnormalities or cytopenia(s), I should discontinue treatment with Nplate™ and consider a bone marrow biopsy, including staining for fibrosis.
  - —Discontinuation of Nplate™ may result in thrombocytopenia of greater severity than was present prior to Nplate™ therapy. This worsened thrombocytopenia resolved within 14 days in the clinical trials.
  - —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 this risk.
  - —Nplate™ may increase the risk for hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS).
- I understand that each patient should be monitored as follows to assure safe use of Nplate™:
  - —Examine the peripheral smear closely to establish a baseline level of cellular morphologic abnormalities.
  - —Monitor CBCs, including platelet counts and peripheral blood smears, weekly until a stable Nplate™ dose has been achieved. Thereafter, CBCs, including platelet counts and peripheral blood smears, should be monitored at least monthly.
  - —If Nplate™ is discontinued, I will obtain weekly CBCs, including platelet counts, for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to treatment guidelines.
- I understand how to properly dose and administer Nplate™ in order to prevent medication errors.
- I understand that I must complete this Nplate™ NEXUS Program Healthcare Provider Enrollment Form to enroll myself in the Nplate™ NEXUS Program (I only need to enroll once).
- I will enroll each patient by assisting in the completion of the Nplate™ NEXUS Program Patient Enrollment Form and completing the Nplate™ NEXUS Program Patient Baseline Data Form. I will complete the Nplate™ NEXUS Program Patient Baseline Data Form at the time of enrollment or within 30 days of patient enrollment. I understand that baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of Nplate™.
- I will provide each patient with the Nplate™ Medication Guide prior to each dose and counsel each patient on the risks and benefits of Nplate™.
- I will complete the Nplate™ NEXUS Program Patient Enrollment Form for each patient: (1) obtain patient's signature acknowledging receipt of Nplate™ Medication Guide, (2) obtain patient's signature authorizing disclosure of health information related to the Nplate™ NEXUS Program, and (3) send the completed Nplate™ NEXUS Program Patient Enrollment Form to the Nplate™ NEXUS Program for patient enrollment.

Nplate™ NEXUS Program Healthcare Provider Enrollment Form

- I will counsel each patient to carry a Patient ID Card and Dosing Tracker that identifies the risks with Nplate™ and contains the Nplate™ NEXUS Program access number.
- I will evaluate the safe use and patient status every 6 months to determine whether the patient should continue Nplate™ and if so, authorize treatment for another 6 months.
- I will notify the Nplate™ NEXUS Program when a patient discontinues Nplate™ by completing the Nplate™ NEXUS Program Patient Discontinuation/ Post-Discontinuation Follow-up Form at the time of Nplate™ discontinuation and 6 months later.
- I will promptly report to the Nplate™ NEXUS Program any adverse events occurring in the course of the use of the drug as described in the Nplate™ NEXUS Program Safety Questionnaire.
- I understand that Amgen will be regularly evaluating compliance with the Nplate™ NEXUS Program, and that Amgen reserves the right to restrict my ability to enroll future patients or take other appropriate measures at any time if I fail to comply with Nplate™ NEXUS Program requirements.

I further understand that I have sole responsibility for all medical judgments and treatments, and have sole responsibility to, prior to Nplate™ administration, counsel each patient on the risks of Nplate™, and provide each patient with all necessary warnings concerning Nplate™.

Physician Signature_____ Date_____

Printed Physician Name_____

Physician Information

Full Name (print) _____

Site Name_____

Address to receive Nplate™ shipment_____

City_____State_____ZIP_____

State License Number_____State Issued_____

DEA Number_____NPI Number (optional)_____Specialty_____

Phone ( )_____–_____ Fax ( )_____–_____ E-mail _____

Office Manager (Purchaser)_____ Phone ( )_____–_____ Fax ( )_____–_____

Indicate your primary treatment setting:

☐ Inpatient institution/hospital ☐ Outpatient facility affiliated with an institution/ hospital

☐ Outpatient facility not affiliated with an institution/hospital

Please fax this completed form to the Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830).

A NEXUS Specialist will follow up to obtain information for communication, shipping, and ordering.

You will receive enrollment confirmation via fax within 48 hours.

For questions regarding the Nplate™ NEXUS Program, call 1-877-NPLATE1 (1-877-675-2831).

Program Use Only: Customer #_____

Nplate™ (romiplostim)
Nexus

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Nplate™(romiplostim)

Nexus

Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

The Nplate™ NEXUS Program connects you with Nplate™ access, support, education, and safety monitoring.

What is the Nplate™ (romiplostim) NEXUS Program?[1]

Nplate™ is only available through the Nplate™ NEXUS (Network of EXperts Understanding and Supporting Nplate™ and patients) Program. This program is designed to promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to assure appropriate use of Nplate™ 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 attempt to normalize platelet counts. Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

The Nplate™ NEXUS Program consists of a patient registry and a requirement for prescribers to complete baseline and periodic safety information for every patient. As a prescriber, you must enroll in the Nplate™ NEXUS Program in order to prescribe Nplate™ by completing the Nplate™ NEXUS Program Healthcare Provider Enrollment Form. Prescribers are required to comply with the following program requirements:

- Read the full prescribing information for Nplate™.
- Understand the approved indication.
- Understand that Nplate™ should not be used in attempt to normalize platelet counts.
- Understand that Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
- Understand the risks associated with Nplate™.
- Understand that each patient should be monitored to assure safe use of Nplate™.
- Understand how to properly dose and administer Nplate™ in order to prevent medication errors.
- Understand that you must complete the Nplate™ NEXUS Program Healthcare Provider Enrollment Form to enroll in the Nplate™ NEXUS Program (only enroll once).

- Enroll each patient by completing the Nplate™ NEXUS Program Patient Enrollment Form and Nplate™ NEXUS Program Patient Baseline Data Form. Complete the Nplate™ NEXUS Program Patient Baseline Data Form at the time of enrollment or within 30 days of patient enrollment. Baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of Nplate™.
- Provide each patient with the Nplate™ Medication Guide prior to each dose and counsel each patient on the risks and benefits of Nplate™.
- Complete the Nplate™ NEXUS Program Patient Enrollment Form with each patient: (1) obtain patient's signature acknowledging receipt of Nplate™ Medication Guide, (2) obtain patient's signature authorizing disclosure of health information related to the Nplate™ NEXUS Program, and (3) send the completed Nplate™ NEXUS Program Patient Enrollment Form to the Nplate™ NEXUS Program for patient enrollment.
- Counsel each patient to carry a Patient ID Card and Dosing Tracker that identifies the risks with Nplate™ and contains the Nplate™ NEXUS Program access number.
- Evaluate the safe use and patient status every 6 months to determine whether the patient should continue Nplate™ and if so, authorize treatment for another 6 months.
- Notify the Nplate™ NEXUS Program when a patient discontinues Nplate™ by completing the Nplate™ NEXUS Program Patient Discontinuation/Post-Discontinuation Follow-up Form at the time of Nplate™ discontinuation and 6 months later.
- Promptly report to the Nplate™ NEXUS Program any adverse events occurring in the course of the use of the drug, as described in the Nplate™ NEXUS Program Safety Questionnaire.
- Understand that Amgen will be regularly evaluating compliance with the Nplate™ NEXUS Program, and that Amgen reserves the right to restrict a healthcare provider's ability to enroll future patients or take other appropriate measures at any time if a healthcare provider fails to comply with Nplate™ NEXUS Program requirements.

Nplate™ (romiplostim)
Nexus
Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

What risks are monitored through the Nplate™ NEXUS Program?[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 4/271 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 ≥ 5 mcg/kg, and six received doses ≥ 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.

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, 4/57 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.

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 ≥ 50 x 10^9/L.

Hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS)

- 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.

Non-ITP populations

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

Medication error due to small volumes administered

- Medication errors may occur because Nplate™ is administered in small volumes, and small differences in dose can have large effects on platelet counts. Healthcare providers should pay special attention to accurate calculation of the dose of Nplate™, transcription of the medication order, and dosing instructions to minimize the risk of medication errors, overdose, and underdose.
- Nplate™ must be administered by the enrolled prescribers or healthcare providers under their direction.

How do I enroll in the Nplate™ NEXUS Program?[1]

Enrollment is simple:

1. Read and understand the Nplate™ package insert and the requirements of the Nplate™ NEXUS Program.
2. Review, complete, and submit the Nplate™ NEXUS Program Healthcare Provider Enrollment Form. Provider enrollment is completed only once.
3. Identify an appropriate patient for Nplate™, educate the patient on the risks and benefits of treatment with Nplate™, make sure that the patient receives the Medication Guide, instruct the patient to read it, and encourage the patient to ask questions when considering Nplate™.
4. Review, complete, and submit the Nplate™ NEXUS Program Patient Enrollment Form, answer all questions, and obtain the patient's signature on the Nplate™ NEXUS Program Patient Enrollment Form. Keep the original, send a copy according to Nplate™ NEXUS Program instructions, and give a copy to the patient.
5. Complete and submit the Nplate™ NEXUS Program Patient Baseline Data Form.

Fax completed forms to 1-877-NPLATE0 (1-877-675-2830) using the forms provided in your Nplate™ NEXUS Program Training Kit, or go online at www.nplate.com to download the forms

The diagram on the next page lays out the steps of the Nplate™ NEXUS Program. Anytime a healthcare provider or patient has a question about Nplate™ use, risks, ITP reimbursement, or other support services, they can call the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831), and a NEXUS Specialist will assist them.

Connecting with Nplate™ (romiplostim) therapy: The five steps of the Nplate™ NEXUS Program

1 Healthcare Provider Enrollment

- Read and understand the Nplate™ package insert and the requirements of the Nplate™ NEXUS Program.
- Review, complete, and submit the Nplate™ NEXUS Program Healthcare Provider Enrollment Form. Provider enrollment is completed only once.
- If desired, you may also order a small safety stock for emergency only. This safety stock can be ordered only by calling 1-877-NPLATE1 (1-877-675-2831).

2 Patient Enrollment

- Identify an appropriate patient for Nplate™, educate the patient on the risks and benefits of treatment with Nplate™, make sure that the patient receives the Medication Guide, instruct the patient to read it, and encourage the patient to ask questions when considering Nplate™.
- Review, complete, and submit the Nplate™ NEXUS Program Patient Enrollment Form, answer all questions, and obtain the patient's signature on the Nplate™ NEXUS Program Patient Enrollment Form. Keep the original, send a copy according to Nplate™ NEXUS Program instructions, and give a copy to the patient.
- Complete and submit the Nplate™ NEXUS Program Patient Baseline Data Form.

3 ITP Reimbursement Assistance (optional)

- Upon enrollment, complete an ITP reimbursement assistance form, if desired.
- NEXUS Specialists can answer questions about Nplate™ and ITP reimbursement at 1-877-NPLATE1 (1-877-675-2831).

4 Fulfillment

- Nplate™ can be ordered through your normal distributor or directly through the Nplate™ NEXUS Program.
- Healthcare providers should only order enough Nplate™ to meet the immediate needs of individual enrolled patients.
- The NEXUS Specialist confirms that you are enrolled in the program and are treating enrolled patients.
- A NEXUS Specialist arranges shipment of Nplate™ to your office. Shipments will usually be received within 48 hours.

5 Support and Follow-up

- Twice a year, a NEXUS Specialist will contact you to verify the enrolled patient roster, collect safety information, and verify whether each patient should continue on Nplate™.

Nplate™ (romiplostim)
Nexus
1-877-NPLATE1 (1-877-675-2831)

How do I order Nplate™?

- Once you and your patient are enrolled in the Nplate™ NEXUS Program, place an order with your preferred distributor, or call 1-877-NPLATE1 (1-877-675-2831), and a NEXUS Specialist will facilitate your order through your normal distributor.
- The NEXUS Specialist confirms that you are enrolled in the program and are treating enrolled patients.
- Your order will be forwarded to the Nplate™ NEXUS Program, where a NEXUS Specialist will call your office to arrange shipment.
- If desired, you may also order a small safety stock for emergency only. This safety stock can be ordered only by calling 1-877-NPLATE1 (1-877-675-2831).
- Nplate™ usually ships within 48 hours in an insulated cold-shipping container to your office.

What do I do for the Nplate™ NEXUS Program during Nplate™ treatment?

- Order Nplate™ for your patients through your primary wholesaler or call 1-877-NPLATE1 (1-877-675-2831). Healthcare providers should only order enough Nplate™ to meet the immediate needs of individual enrolled patients.
- Provide each patient with the Medication Guide prior to each Nplate™ injection.
- Promptly report any adverse events associated with the use of Nplate™ to the Nplate™ NEXUS Program at 1-877-675-2831 or FDA's MedWatch Program at 1-800-FDA-1088.
- Twice a year, verify your patient roster, then complete and submit an Nplate™ NEXUS Program Safety Questionnaire for each patient by fax (1-877-NPLATE0 [1-877-675-2830]), or phone (1-877-NPLATE1 [1-877-675-2831]). You will verify that each patient should continue on Nplate™.
- For any report of a serious adverse event, Amgen will follow up for more information. You can provide more detailed information by submitting the MedWatch form by fax (1-877-NPLATE0 [1-877-675-2830]), or giving the information over the phone (1-877-NPLATE1 [1-877-675-2831]).

What do I do if a patient discontinues Nplate™ treatment?

- Complete and submit the Nplate™ NEXUS Program Patient Discontinuation/Post-Discontinuation Follow-up Form at time of discontinuation and 6 months later. The form can be submitted by fax (1-877-NPLATE0 [1-877-675-2830]), or phone (1-877-NPLATE1 [1-877-675-2831]).
- Call 1-877-NPLATE1 (1-877-675-2831) to inquire about product returns.

What ITP reimbursement support is available?

The Nplate™ NEXUS Program will provide optional ITP reimbursement assistance to patients and healthcare providers.

ITP reimbursement services include:

- Verifying insurance coverage
- Assisting with alternative funding options
- Assistance with prior authorizations, claims, denials, and appeals

What other risks are associated with Nplate™?[1]

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.
- To detect antibody formation, submit blood samples to Amgen at 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.

Common adverse drug reactions

- 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.
- Most common adverse reactions (≥ 5% higher patient incidence in Nplate™ versus placebo) were 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%), and Paresthesia (6%, 0%).

See the following pages for hospital and institutional enrollment.

For institutional enrollment only (not for individual practices)

Hospital and Institutional Enrollment

The Nplate™ NEXUS Program offers the flexibility of institutional enrollment

Hospitals and other healthcare institutions may enroll by submitting an Nplate™ NEXUS Program Institution Enrollment Form. Upon enrollment, an institution may designate an Nplate™ NEXUS Program point of contact for the institution. The designated person may be a hospital administrator, pharmacy director, clinical pharmacist, or any staff member the institution deems appropriate to internally coordinate Nplate™ NEXUS Program activities.

During enrollment, the designated person will complete an Nplate™ NEXUS Program Institution Enrollment Form agreeing to the following:

- Develop a system, order sets, protocols, or other measures to ensure that Nplate™ is only dispensed to inpatients and outpatients (eg, in a clinic) after verifying that the prescribing healthcare provider and patient are enrolled in the Nplate™ NEXUS Program;
- Train and provide educational materials to appropriate staff responsible for prescribing, dispensing, and administering Nplate™ regarding the safe and appropriate use of Nplate™, program monitoring requirements (including dispensing a Medication Guide with each dose), program adverse event reporting requirements, and institution documentation requirements;
- Develop a system to ensure patients started on Nplate™ as inpatients are transitioned to an outpatient healthcare provider that is enrolled (or will be enrolled) in the Nplate™ NEXUS Program; and
- Develop a process and system to track Nplate™ NEXUS Program compliance and cooperate with periodic audits to assure that Nplate™ is used in accordance with the program requirements. Product tracking includes the following information:
  - Name and unique identification number of the enrolled prescribing healthcare provider
  - Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate™
  - Date of each Nplate™ order (including number of vials ordered and vial sizes)
  - Number of Nplate™ vials, vial sizes, and date of each dose given to each patient
  - Overall inventory for the set period of time including the total number of vials ordered, dispensed, and in stock

The designated contact will receive the Nplate™ NEXUS Program Training Kits for in-house training along with copies of the Nplate™ Medication Guide. NEXUS Specialists and Amgen representatives will be available as resources to institutions and assist healthcare providers in the enrollment and training. Please note: In addition to institutional enrollment, all individual healthcare providers must be enrolled in the Nplate™ NEXUS Program in order to prescribe Nplate™.

Amgen will be regularly evaluating program compliance to ensure that program objectives are met. Amgen reserves the right to terminate an institution enrollment at any time based upon the institution's noncompliance with program requirements, or take other appropriate measures to assure that program objectives are met.

Ordering Nplate™

Once an institution and patient(s) are enrolled, an institution will receive an enrollment confirmation. This enrollment must be completed only once. Ordering and billing for Nplate™ will occur through your primary wholesaler. A NEXUS Specialist will arrange shipment directly to the institution.

If desired, you may also order a small safety stock for emergency only. This safety stock can be ordered only by calling 1-877-NPLATE1 (1-877-675-2831).

Prescribing Nplate™

When a healthcare provider enrolled in the Nplate™ NEXUS Program identifies and prescribes Nplate™ to an appropriate patient, a designated hospital staff member will check with the Nplate™ NEXUS Program to verify that the patient was previously enrolled in the program. An Nplate™ NEXUS Program Patient Enrollment Form must be completed for any new patient.

Record-keeping

Enrolled institutions will be required to maintain drug accountability and reconciliation records. This may include, at minimum, the following information:

- Name and unique identification number of the enrolled prescribing healthcare provider
- Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate™
- Date of each Nplate™ order (including number of vials ordered and vial sizes)
- Number of Nplate™ vials, vial sizes, and date of each dose given to each patient
- Overall inventory for the set period of time including the total number of vials ordered, dispensed, and in stock

Monitoring patient safety with the Nplate™ NEXUS Program

The Nplate™ NEXUS Program is designed to promote informed risk-benefit decisions and includes a system of reminders, guides, and databases to monitor patient safety. For instance, the Medication Guide presents information on the risks of Nplate™ in patient-friendly language. Every new patient will be educated on the content of the Medication Guide including the risk-benefit profile of Nplate™.

Healthcare providers submit baseline patient data as patients begin Nplate™ therapy. The purpose of this data collection is to establish the long-term safety and safe use of Nplate™ through periodic monitoring. The registry also includes available baseline patient data.

Twice a year, a NEXUS Specialist will contact the healthcare provider to verify his/her enrolled patient roster and collect safety information. The healthcare provider (or staff under his/her direction) will be asked to complete a safety questionnaire for each patient via fax or phone. This questionnaire asks whether the patient remains on Nplate™ therapy and whether the patient has experienced side effects. The NEXUS Specialist will log any adverse events and discontinuation information into a registry database. Whenever a serious adverse event is reported, someone from the Nplate™ NEXUS Program or Amgen Global Safety will follow up by contacting the reporting provider or representative to obtain additional information.

Please call the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831) to answer any questions or for additional materials. You may also go to www.nplate.com for information and downloadable materials.

Reference: 1. Nplate™ [prescribing information]. Thousand Oaks, CA: Amgen; 2008.

Nplate™(romiplostim)

Nexus

Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

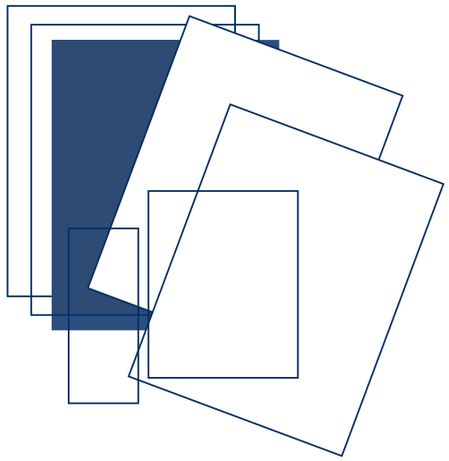
The Nplate™ NEXUS Program connects you with Nplate™ access, support, education, and safety monitoring.

- Amgen is committed to quality patient care. The Nplate™ NEXUS Program is designed to promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to assure appropriate use of Nplate™ and to monitor safety in order to provide quality patient care.

What the Nplate™ NEXUS Program means to you:

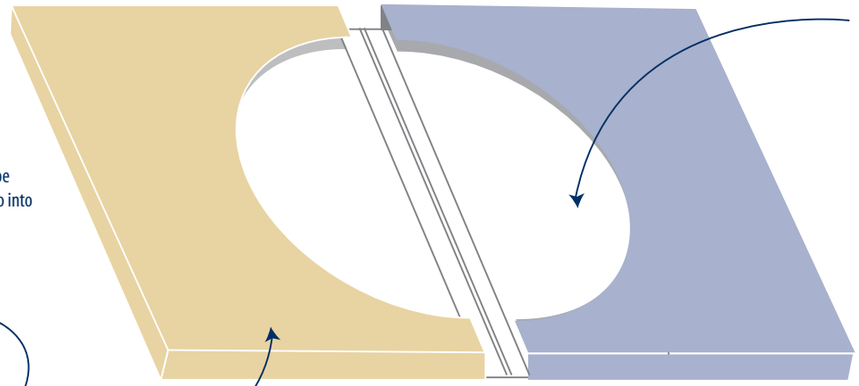
- Healthcare provider and patient enrollment
- Education for healthcare providers who intend to prescribe Nplate™, healthcare providers under their direction, and patients
- Monitoring program to manage patient safety

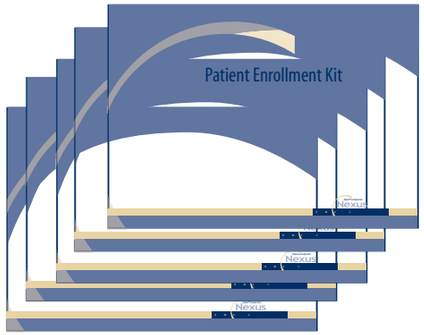
Nplate™ is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Nplate™ should not be used in an attempt to normalize platelet counts.



Healthcare provider (HCP) materials will be contained in an envelope that will then go into the HCP side of the folder.
Tabbed dividers will separate the pieces.
Tabbed sections will be labeled:

- Program Information
- Prescribing Information
- Dosing & Administration
- Enrollment Forms
- Safety & Monitoring Forms

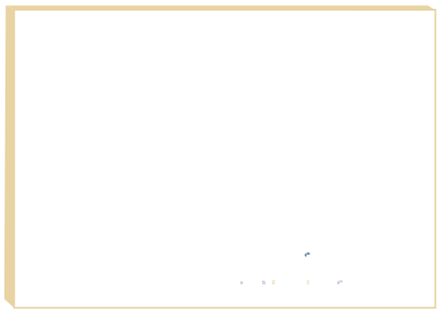




Five Patient Enrollment Kits go into the patient side.

Each Patient Enrollment Kit includes:

- Nplate™ NEXUS Program Patient/Caregiver Introductory Letter
- "What is Nplate™ NEXUS?"—a brochure for Nplate™ patients and caregivers, including the Medication Guide
- Nplate™ Prescribing Information and Medication Guide
- Patient ID Card and Dosing Tracker
- Nplate™ NEXUS Program Patient Enrollment Form
- Nplate™ NEXUS Program Patient Baseline Data Form



Materials in the Healthcare Provider Information folder include:

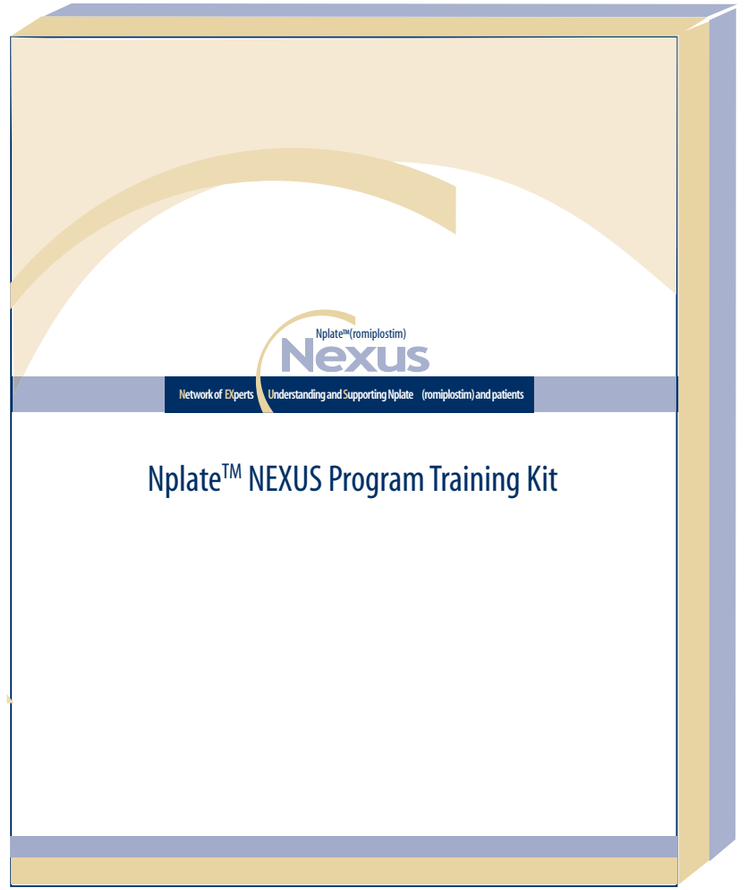
- Nplate™ NEXUS Program Healthcare Provider Introductory Letter
- USB drive with electronic versions of all forms
- Nplate™ NEXUS Program Brochure
- Nplate™ Prescribing Information and Medication Guide
- Nplate™ Dose Calculator
- Nplate™ NEXUS Program Healthcare Provider Enrollment Form
- Nplate™ NEXUS Program Patient Enrollment Form
- Nplate™ NEXUS Program Institution Enrollment Form
- ITP Reimbursement Assistance Form
- Nplate™ NEXUS Program Patient Baseline Data Form
- Nplate™ NEXUS Program Safety Questionnaire
- Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form
- MedWatch form

NEXUS MATERIAL HOLDER
Two-sided "book" folder

The folder is 11.75" high x 9" wide and 1.5" to 2" deep, and is designed to sit upright on a shelf, like a book.

The materials fit in dimensional pockets.
Left side for healthcare provider materials (1 set), and right side for patient materials (5 sets).

A "jump drive" will be incorporated into the design to store electronic files of the forms.



Nplate™ romiplostim Dose Calculator

Use the table below as a quick way to compute injection volume, based on dose and initial weight.

Patient weight (kg)	Dose (mcg/kg)									
	1	2	3	4	5	6	7	8	9	10
	Total injection volume (mL) required for total dose									

Patient's total dose in mcg = patient's initial weight in kg x dose in mcg/kg.

Injection volume in mL = patient's total dose / 500 mcg/mL

Calculate initial dose:

1. Initial dose for Nplate™ is 1 mcg/kg based on **actual body weight**.
2. Determine patient's weight in kilograms.
3. Refer to window above to achieve total injection volume required.

Subsequent doses:

1. Determine patient's platelet count and previous week's dose.
2. Identify weight in kilograms at **initiation** of Nplate™ therapy.
3. Refer to dose adjustment chart below to determine how to adjust dose in mcg/kg.
4. Refer to window above to achieve total injection volume required.
5. Assess complete blood counts (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.

Platelet count ($\times 10^9$/L)	Adjust the dose as follows:
< 50	Increase the dose by 1 mcg/kg.
> 200 for 2 consecutive weeks	Reduce the dose by 1 mcg/kg.
> 400	Do not dose. Assess 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.

Do not exceed a weekly maximum dose of 10 mcg/kg.

Nplate™ should continue to be administered weekly unless a platelet count of $> 400 \times 10^9$/L is achieved.

Please see Important Safety Information inside flap.

Nplate™ romiplostim

Directions for dose administration and reconstitution

- Use the lowest dose of Nplate™ to achieve and maintain a platelet count of $\geq 50 \times 10^9$/L as necessary to reduce the risk for bleeding.
- Administer Nplate™ as a weekly subcutaneous injection with dose adjustments based on platelet count response.
- 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.
- Injection volume may be very small. Use a syringe with graduations to 0.01 mL.
- Only prescribers enrolled in the Nplate™ NEXUS Program may prescribe Nplate™. Nplate™ must be administered by the enrolled prescribers or healthcare providers under their direction.

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. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Nplate™.

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.

Important Safety Information

Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation.

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 ≥ 5 mcg/kg, and 6 received doses ≥ 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.

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 two weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines.

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.

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.
- 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.

Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS)

- 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 syndromes (MDS), 11 patients were reported as having possible disease progression, among whom 4 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.

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™.

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).

General Safety

- 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.
- Most common adverse reactions ($\geq 5\%$ higher patient incidence in Nplate™ versus placebo) were 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%), and Paresthesia (6%, 0%).
- As with all therapeutic proteins, patients may develop antibodies to the therapeutic protein.

Please see accompanying Prescribing Information and Medication Guide.

Nplate™ romiplostim

- Nplate™ can only be reconstituted with preservative-free Sterile Water for Injection, USP. Do not use bacteriostatic water for injection.
- Nplate™ is available in 250 or 500 mcg in single-use vials. Refrigerate lyophilized Nplate™ and protect from light. Do not freeze.
- Each vial of Nplate™ is for single use only and contains no preservatives.
  —Administer reconstituted product within 24 hours (at room temperature or 2° to 8° [36° to 46°F]).
- Reconstituted Nplate™ must also be protected from light.
- Discard ANY unused portion.
  —Do not pool unused portions from vials.
  —Do not use the vial more than one time.
- Nplate™ is a protein—**DO NOT SHAKE** during reconstitution.

Please see Important Safety Information inside flap.

Nplate™ romiplostim

Steps for reconstitution and administration

Use appropriate aseptic technique when performing the following steps:

1. Remove plastic caps from sterile water for injection and the lyophilized powder vial. Use a new alcohol swab to clean each vial stopper.
2. Using a sterile syringe, draw up 1.2 mL of Sterile Water for Injection, USP to reconstitute a 500-mcg vial or 0.72 mL to reconstitute a 250-mcg vial. Be sure to remove all air bubbles.
3. **Slowly** and gently expel the Sterile Water for Injection, USP into the vial containing Nplate™. The diluent should be directed onto the lyophilized cake.
4. Gently swirl the vial to evenly wet the powder and reconstitute Nplate™. Avoid excess or vigorous agitation, as this is a protein. **DO NOT SHAKE.** The solution should be clear, colorless, and essentially free of visible particles before it is ready for injection. If there is particulate matter and/or discoloration, do not administer Nplate™.
5. Using a new syringe with 0.01 mL graduations, insert the needle through the rubber stopper of the vial containing reconstituted product and then invert the vial. Position the needle tip in the solution and withdraw the correct volume of Nplate™ required for the patient's dose into the syringe. Ensure there are no air bubbles in the syringe.
6. Using a new needle with the appropriate gauge (25, 27, 29, 31), a subcutaneous Nplate™ injection may now be given.

Nplate™ is supplied as a sterile, preservative-free, white lyophilized powder in single-use vials of two different sizes.

Reconstitution of Nplate™ Single-Use Vials	Total Vial Content of Romiplostim		Sterile Water for Injection, USP		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, USP.
Do not use bacteriostatic water for injection.

This tool provides assistance but does not replace your clinical judgment in determining appropriate dose by the prescriber for his or her patient.

Please see Important Safety Information inside flap.

PULL

40	0.08	0.16	0.24	0.32	0.4	0.48	0.56	0.64	0.72	0.8
45	0.09	0.18	0.27	0.36	0.45	0.54	0.63	0.72	0.81	0.9
50	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
55	0.11	0.22	0.33	0.44	0.55	0.66	0.77	0.88	0.99	1.1
60	0.12	0.24	0.36	0.48	0.6	0.72	0.84	0.96	1.08	1.2
65	0.13	0.26	0.39	0.52	0.65	0.78	0.91	1.04	1.17	1.3
70	0.14	0.28	0.42	0.56	0.7	0.84	0.98	1.12	1.26	1.4
75	0.15	0.3	0.45	0.6	0.75	0.9	1.05	1.2	1.35	1.5
80	0.16	0.32	0.48	0.64	0.8	0.96	1.12	1.28	1.44	1.6
85	0.17	0.34	0.51	0.68	0.85	1.02	1.19	1.36	1.53	1.7
90	0.18	0.36	0.54	0.72	0.9	1.08	1.26	1.44	1.62	1.8
95	0.19	0.38	0.57	0.76	0.95	1.14	1.33	1.52	1.71	1.9
100	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2
105	0.21	0.42	0.63	0.84	1.05	1.26	1.47	1.68	1.89	2.1
110	0.22	0.44	0.66	0.88	1.1	1.32	1.54	1.76	1.98	2.2
115	0.23	0.46	0.69	0.92	1.15	1.38	1.61	1.84	2.07	2.3
120	0.24	0.48	0.72	0.96	1.2	1.44	1.68	1.92	2.16	2.4
125	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.25	2.5
130	0.26	0.52	0.78	1.04	1.3	1.56	1.82	2.08	2.34	2.6
135	0.27	0.54	0.81	1.08	1.35	1.62	1.89	2.16	2.43	2.7
140	0.28	0.56	0.84	1.12	1.4	1.68	1.96	2.24	2.52	2.8
145	0.29	0.58	0.87	1.16	1.45	1.74	2.03	2.32	2.61	2.9
150	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3

Nplate™ (romiplostim)
Nexus
1-877-NPLATE1 (1-877-675-2831)

- Prescribing Information
- Medication Guide

Welcome to Nplate™ (romiplostim) NEXUS

The Nplate™ NEXUS Program Connects You With Nplate™ Access, Support, Education, and Safety Monitoring.

Amgen is committed to encouraging quality patient care. The Nplate™ NEXUS program is designed to facilitate provider education and monitor safety to assure quality patient care.

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.

IMPORTANT SAFETY INFORMATION

Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation. Additional risks include Bone Marrow Fibrosis, Thrombotic/Thromboembolic Complications, Lack or Loss of Response to Nplate™, and Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS).

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

Nplate™ is available only through a restricted distribution program called the Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

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Oncology

Nplate™ (romiplostim)
Nexus
1-877-NPLATE1 (1-877-675-2831)

About Nplate™ NEXUS

What Is the Nplate™ (romiplostim) NEXUS Program?

- Prescribing Information
- Medication Guide

Nplate™ is only available through the Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate™ and patients) Program. This program is designed to promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to assure appropriate use of Nplate™ in patients with chronic 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. It should not be used in an attempt to normalize platelet counts. Nplate™ is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP.

The Nplate™ NEXUS Program consists of a patient registry and a requirement for prescribers to complete baseline and periodic safety information for every patient. As a prescriber, you must enroll in the Nplate™ NEXUS Program in order to prescribe Nplate™ by completing the Nplate™ NEXUS Program Healthcare Provider Enrollment Form. Prescribers are required to comply with the following program requirements:

- Read the full prescribing information for Nplate™.
- Understand the approved indication.
- Understand that Nplate™ should not be used in an attempt to normalize platelet counts.
- Understand that Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.
- Understand the risks associated with Nplate™.
- Understand that each patient should be monitored to assure safe use of Nplate™.
- Understand how to properly dose and administer Nplate™ in order to prevent medication errors.
- Understand that you must complete this Nplate™ NEXUS Program Healthcare Provider Enrollment Form to enroll in the Nplate™ NEXUS Program (only enroll once).
- Enroll each patient by completing the Nplate™ NEXUS Program Patient Enrollment Form and Nplate™ NEXUS Program Patient Baseline Data Form. Complete the Nplate™ NEXUS Program Patient Baseline Data Form at the time of enrollment or within 30 days of patient enrollment. Baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of Nplate™.
- Provide each patient with the Nplate™ Medication Guide prior to each dose and counsel each patient on the risks and benefits of Nplate™.
- (1) Complete the Nplate™ NEXUS Program Patient Enrollment Form for each patient, (2) obtain patient's signature authorizing disclosure of health information related to the Nplate™ NEXUS Program, and (3) send the completed Nplate™ NEXUS Program Patient Enrollment Form to the Nplate™ NEXUS Program for patient enrollment.
- Counsel each patient to carry a Patient ID Card and Dosing Tracker that identifies the risks with Nplate™ and contains the Nplate™ NEXUS Program access number.
- Evaluate the safe use and patient status every 6 months to determine whether the patient should continue Nplate™ and if so, authorize treatment for another 6 months.
- Notify the Nplate™ NEXUS Program when a patient discontinues Nplate™ by completing the Nplate™ NEXUS Program Patient Discontinuation Form/Post-Discontinuation Follow-up Form at the time of Nplate™ discontinuation and 6 months later.
- Promptly report to the Nplate™ NEXUS Program any adverse events occurring in the course of the use of the drug as described in the Nplate™ NEXUS Program Safety Questionnaire.
- Understand that Amgen will be regularly evaluating compliance with the Nplate™ NEXUS Program, and that Amgen reserves the right to restrict your ability to enroll future patients or take other appropriate measures at any time if you fail to comply with Nplate™ NEXUS Program requirements.

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Enrollment

How Do I Enroll in the Nplate™ NEXUS Program?[1]

Prescribing Information
Medication Guide

Enrollment Is Simple:

1. Read and understand the Nplate™ package insert and the requirements of the Nplate™ NEXUS Program.
2. Review, complete, and submit the Nplate™ NEXUS Program Healthcare Provider Enrollment Form. Provider enrollment is completed only once.
3. Identify an appropriate patient for Nplate™, educate the patient on the risks and benefits of treatment with Nplate™, make sure that the patient receives the Medication Guide, instruct the patient to read it, and encourage the patient to ask questions when considering Nplate™.
4. Review, complete, and submit the Nplate™ NEXUS Program Patient Enrollment Form, answer all questions, and obtain the patient's signature on the Nplate™ NEXUS Patient Program Enrollment Form. Keep the original, send a copy according to Nplate™ NEXUS Program instructions, and give a copy to the patient.
5. Complete and submit the Nplate™ NEXUS Program Patient Baseline Data Form. Fax completed forms to 1-877-NPLATE0 (1-877-675-2830) using the forms provided in your Nplate™ NEXUS Program Training Kit, or go online at www.nplate.com to download the forms.

Hospital and Institutional Enrollment (not for individual practices)
The Nplate™ NEXUS Program offers the flexibility of institutional enrollment.
Hospitals and other healthcare institutions may enroll by submitting an Nplate™ NEXUS Program Institution Enrollment Form. Upon enrollment, an institution may designate an Nplate™ NEXUS Program point of contact for the institution. The designated person may be a hospital administrator, pharmacy director, clinical pharmacist, or any staff member the institution deems appropriate to internally coordinate Nplate™ NEXUS Program activities.

During enrollment, the designated person will complete an Nplate™ NEXUS Program Institution Enrollment Form agreeing to the following:

- Develop a system, order sets, protocols, or other measures to ensure that Nplate™ is only dispensed to inpatients and outpatients (eg, in a clinic) after verifying that the prescribing healthcare provider and patient are enrolled in the Nplate™ NEXUS Program;
- Train and provide educational materials to appropriate staff responsible for prescribing, dispensing, and administering Nplate™ regarding the safe and appropriate use of Nplate™, program monitoring requirements (including dispensing the medication guide with each dose), program adverse event reporting requirements, and institution documentation requirements;
- Develop system to ensure patients started on Nplate™ as inpatients are transitioned to an outpatient healthcare provider that is enrolled (or will be enrolled) in the Nplate™ NEXUS Program; and
- Develop a process and system to track Nplate™ NEXUS Program compliance and cooperate with periodic audits to assure that Nplate™ is used in accordance with the program requirements. Product tracking includes the following information:
  - Name and unique identification number of enrolled prescribing healthcare provider
  - Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate™
  - Date of each Nplate™ order (including number of vials ordered and vial size)
  - Number of Nplate™ vials, vial sizes, and date of each dose given to each patient
  - Overall inventory for the set period of time including the total number of vials ordered, dispensed, and in stock

The designated contact will receive the Nplate™ NEXUS Program Training Kits for in-house training along with copies of the Nplate™ Medication Guide. NEXUS Specialists and Amgen representatives will be available as resources to institutions and assist healthcare providers in enrollment and training.

Please Note: *In addition, to institutional enrollment, all individual healthcare providers must be enrolled in the Nplate™ NEXUS Program in order to prescribe Nplate™.*

Amgen will be regularly evaluating program compliance to ensure that program objectives are met. Amgen reserves the right to terminate an institutional enrollment at any time based upon the institution's non-compliance with program requirements, or take other appropriate measures to assure that program objectives are met.

- Nplate™ NEXUS Program Healthcare Provider Enrollment Form
- Nplate™ NEXUS Patient Enrollment Form
- Nplate™ NEXUS Institution Enrollment Form

Back to top

The following diagram lays out the steps of the Nplate™ NEXUS Program. Any time healthcare providers or patients have a question about Nplate™ use, risks, ITP reimbursement, or other support services, they can call the NEXUS Program at 1-877-NPLATE1 (1-877-675-2831), and a NEXUS Specialist will provide assistance.

Connecting With Nplate™ (romiplostim) Therapy: The 5 Steps of the Nplate™ NEXUS Program

Back to top

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IMPORTANT SAFETY INFORMATION

Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation. Additional risks include Bone Marrow Fibrosis, Thrombotic/Thromboembolic Complications, Lack or Loss of Response to Nplate™, and Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS).

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

Nplate™ is available only through a restricted distribution program called the Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

Nplate™ (romiplostim) Nexus

1-877-NPLATE1 (1-877-675-2831)

- Prescribing Information
- Medication Guide

Ordering Nplate™

Answering Your Questions About the Nplate™ (romiplostim) NEXUS Program

How Do I Order Nplate™?

- Once you and your patient are enrolled in the Nplate™ NEXUS Program, place an order with your preferred distributor, or call 1-877-NPLATE1 (1-877-675-2831), and a NEXUS Specialist will facilitate your order through your normal distributor.
- The NEXUS Specialist confirms that you are enrolled in the program and are treating enrolled patients.
- Your order will be forwarded to the Nplate™ NEXUS Program, where a NEXUS Specialist will call your office to arrange shipment.
- If desired, you may also order a small safety stock for emergency only. This safety stock can be ordered only by calling 1-877-NPLATE1 (1-877-675-2831).
- Nplate™ usually ships within 48 hours in an insulated cold-shipping container to your office.

Hospital and Institutional Ordering Nplate™

Once an institution and patient(s) are enrolled, an institution will receive an enrollment confirmation. This enrollment must be completed only once. Ordering and billing for Nplate™ will occur through your primary wholesaler. A NEXUS Specialist will arrange shipment directly to the institution.

If desired, you may also order a small safety stock for emergency only. This safety stock can be ordered only by calling 1-877-NPLATE1 (1-877-675-2831).

Prescribing Nplate™

When a healthcare provider enrolled in the Nplate™ NEXUS Program identifies and prescribes Nplate™ to an appropriate patient, a designated hospital staff member will check with the Nplate™ NEXUS program to verify that the patient was previously enrolled in the program. An Nplate™ NEXUS Program Patient Enrollment Form must be completed for any new patient.

Record Keeping

Enrolled institutions will be required to maintain drug accountability and reconciliation records. This may include, at minimum, the following information:

- Name and unique identification number of enrolled prescribing healthcare provider
- Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate™
- Date of each Nplate™ order (including number of vials ordered and vial size)
- Number of Nplate™ vials, vial sizes, and date of each dose given to each patient
- Overall inventory for the set period of time including the total number of vials ordered, dispensed, and in stock

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.

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In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

AMGEN Oncology

Support & Follow-Up

What Do I Do for the Nplate™ NEXUS Program During Nplate™ Treatment?

▸ Prescribing Information
▸ Medication Guide

- Order Nplate™ for your patients through your primary wholesaler or call 1-877-NPLATE1 (1-877-675-2831). Healthcare providers should only order enough Nplate™ to meet the immediate needs of individual enrolled patients.
- Provide each patient with the Medication Guide prior to each Nplate™ injection.
- Promptly report any adverse events associated with the use of Nplate™ to the Nplate™ NEXUS Program at 1-877-675-2831 or FDA's MedWatch Program at 1-800-FDA-1088.
- Twice a year, verify your patient roster, then complete and submit an Nplate™ NEXUS Program Safety Questionnaire for each patient by fax (1-877-NPLATE0 [1-877-675-2830]) or phone (1-877-NPLATE1 [1-877-675-2831]).You will verify that each patient should continue on Nplate™.
- For any report of an adverse event, Amgen will follow up for more information. You can provide more detailed information by submitting the MedWatch form by fax (1-877-NPLATE0 [1-877-675-2830]) or giving the information over the phone (1-877-NPLATE1 [1-877-675-2831]).

▸ Nplate™ NEXUS Program Safety Questionnaire

▸ The FDA Safety Information and Adverse Event Reporting Program – MedWatch Form

What Do I Do If a Patient Discontinues Nplate™ Treatment?

- Complete and submit the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form. The form can be submitted by fax (1-877-NPLATE0 [1-877-675-2830]) or phone (1-877-NPLATE1 [1-877-675-2831]).
- Call 1-877-NPLATE1 (1-877-675-2831) to inquire about product returns.

▸ Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form

What ITP Reimbursement Support Is Available?

The Nplate™ NEXUS Program will provide optional ITP reimbursement assistance to patients and healthcare providers.

ITP reimbursement services include:
– Verifying insurance coverage
– Assisting with alternative funding options
– Assistance with prior authorizations, claims, denials, and appeals

▸ Go to the Nplate™ Reimbursement Connection page

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Risk Monitoring

Monitoring Patient Safety With the Nplate™ NEXUS Program

Prescribing Information
Medication Guide

The Nplate™ NEXUS Program is designed to promote informed risk-benefit decisions and includes a system of reminders, guides, and databases to monitor patient safety. For instance, the Medication Guide presents information on the risks of Nplate™ in patient-friendly language. Every new patient will be educated on the content of the Medication Guide including the risk-benefit profile of Nplate™.

Healthcare providers submit baseline patient data as patients begin Nplate™ therapy. The purpose of this data collection is to establish the long-term safety and safe use of Nplate™ through periodic monitoring.The registry also includes available baseline patient data.

Twice a year, a NEXUS Specialist will contact the healthcare provider to verify his/her enrolled patient roster and collect safety information. The healthcare provider (or staff under his/her direction) will be asked to complete a safety questionnaire for each patient via fax or phone. This questionnaire asks whether the patient remains on Nplate™ therapy and whether the patient has experienced side effects. The NEXUS Specialist will log any adverse events and discontinuation information into a registry database. Whenever a serious adverse event is reported, someone from the Nplate™ NEXUS Program or Amgen Global Safety will follow up by contacting the reporting provider or representative to obtain additional information.

Please call the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831) to answer any questions or for additional materials. You may also go to www.nplate.com for information and downloadable materials.

What Risks Are Monitored Through the Nplate™ NEXUS Program?

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 ≥ 5 mcg/kg and six received doses ≥ 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.

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, 4/57 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.

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 ≥ 50 x 10^9/L.

Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS)

- Nplate™ stimulation of the thrombopoietin (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.

Non-ITP Populations

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

Medication Error Due to Small Volumes Administered

- Medication errors may occur because Nplate™ is administered in small volumes, and small differences in dose can have large effects on platelet counts. Healthcare providers should pay special attention to accurate calculation of the dose of Nplate™, transcription of the medication order, and dosing instructions to minimize the risk of medication errors, overdose, and underdose.
- Nplate™ must be administered by the enrolled prescribers or healthcare providers under their direction.

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What Other Risks Are Associated With Nplate™?

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.
- To detect antibody formation, submit blood samples to Amgen at 1-800-772-6436. Amgen will assay these samples for antibodies to Nplate™ and thrombopoietin.
- 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.

Common Adverse Drug Reactions

- 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.
- Most common adverse reactions (≥ 5% higher patient incidence in Nplate™ versus placebo) were 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%), and Paresthesia (6%, 0%).

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Nplate™ (romiplostim)
Nexus
1-877-NPLATE1 (1-877-675-2831)

Resources

- Prescribing Information
- Medication Guide

For your convenience, all our forms can be found below. Take a moment and bookmark this page for future visits. . .

Healthcare Professional

- Nplate™ NEXUS Program Healthcare Provider Enrollment Form
- Nplate™ NEXUS Program Institution Enrollment Form
- The FDA Safety Information and Adverse Event Reporting Program – MedWatch Form
- Nplate™ NEXUS Program Healthcare Professional Brochure
- Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form
- Nplate™ NEXUS Program: Bone Marrow Reticulin/Bone Marrow Fibrosis Form
- Nplate™ NEXUS Program: Hematological Malignancy/MDS Form
- Nplate™ NEXUS Program: Medication Errors Associations and Serious Outcomes Form
- Nplate™ NEXUS Program: Worsened Thrombocytopenia after Cessation of Treatment with Nplate™ Form
- Nplate™ NEXUS Program: Thrombotic/Thromboembolic Complications Form

Patient

- Nplate™ NEXUS Program Patient Enrollment Form
- Nplate™ NEXUS Program Patient Brochure
- Nplate™ NEXUS Program Safety Questionnaire
- Nplate™ NEXUS Program Patient Baseline Data Form

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AMGEN
Oncology

Nplate™ (romiplostim)
REMS
Nplate™ NEXUS PROGRAM CALL CENTER

The Nplate™ NEXUS Program includes a call center component. The call center will be staffed by NEXUS Specialists from a third party organization that are agents of Amgen. The NEXUS Specialists will be specifically trained on Nplate™ NEXUS Program enrollment, fulfillment and safety data collection. The NEXUS Specialists will be responsible for processing of patient, HCP, and Hospital/Institutional enrollments as well as facilitating ordering and distribution of Nplate™. The NEXUS Specialists are also responsible for coordinating the intake and completion of the Nplate™ NEXUS Program Patient Baseline Data Form, Nplate™ NEXUS Program Safety Questionnaire, the risk-specific adverse event report forms and the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form, as well as intake of initial spontaneous adverse reporting.

The Nplate™ NEXUS Program IVR system will include an emergency prompt that will be staffed 24 hours a day, 7 days a week to manage urgent requests for Nplate™ for patients already enrolled to the program.

Nplate™ (romiplostim)
REMS
PROCEDURE FOR PRESCRIBER DISTRIBUTION (HCPs/HOSPITAL/INSTITUTION)

Objective:
To describe the procedure utilized to restrict distribution of Nplate™ (romiplostim) to HCPs or Institutions that are enrolled to the Nplate™ NEXUS Program in accordance with the procedure set forth by the Nplate™ NEXUS Program.

The following sections outline the detailed procedures for:

- Enrollment in the Nplate™ NEXUS Program for HCP, Hospital/Institution, and patient
- Ordering Nplate™
- Nplate™ fulfillment
  - Hospital/Institution dispensing
  - Treatment continuation
  - Treatment discontinuation
  - Safety stock and emergency shipments

1. Enrollment in the Nplate™ NEXUS Program

1.1 Healthcare Provider Enrollment

HCPs (inclusive of physicians and other HCPs granted prescribing privileges) who wish to prescribe Nplate™ in an inpatient or outpatient setting will enroll in the Nplate™ NEXUS Program by completing an Nplate™ NEXUS Program Healthcare Provider Enrollment Form, which is included in the Nplate™ NEXUS Program Training Kit. By signing the form, HCPs agree to comply with the program requirements as stated in the Nplate™ NEXUS Program Healthcare Provider Enrollment Form.

HCPs will either fax the completed Nplate™ NEXUS Healthcare Provider Program Enrollment Form to the Nplate™ NEXUS Program or, once available, complete an online form to enroll. HCPs will receive an enrollment confirmation via fax or e-mail 48 hours or sooner after enrolling in the program.

Once available, HCPs will have an option to enroll online and enter patient data online on the Nplate™ NEXUS Program website. All data entered into this system will be password protected and tested for security.

1.2 Hospital/Institutional Enrollment

In addition to individual HCP enrollment, a hospital/institution that will order Nplate™ through a central pharmacy for inpatient or outpatient use will need to enroll in the Nplate™ NEXUS Program in order to receive Nplate™. Institutions will be able to enroll online, once available, or by fax. Each enrolling institution may designate a person to be the point of contact for the institution. The designated person may be a hospital administrator, pharmacy director, clinical pharmacist, or any staff member the institution deems appropriate to internally coordinate the logistics of the program.

In order to enroll, the designated person will complete an Nplate™ NEXUS Program Institution Enrollment Form attesting to program requirements. In addition to the enrollment of a designated person at a hospital, each healthcare provider who prescribes Nplate™ needs to be enrolled in the Nplate™ NEXUS Program.

Prior to enrollment of the institution, the designated contact will receive the Nplate™ NEXUS Program Training Kits for in-house training along with copies of the Nplate™ Medication Guide. Amgen RMLs and sales representatives will be available as resources to institutions and assist in the enrollment and training process.

1.3 Patient Enrollment

The enrolled HCP will introduce a patient to the Nplate™ NEXUS Program and review with the patient the Nplate™ Medication Guide and the risk-benefit information for Nplate™. The enrolled HCP will assist the patient in the completion of Nplate™ NEXUS Program Patient Enrollment Form as stated in the Nplate™ NEXUS Program Healthcare Provider Enrollment Form and the Nplate™ NEXUS Program Brochure. Patients will sign an Nplate™ NEXUS Program Patient Enrollment Form acknowledging their review of the Nplate™ Medication Guide and agreeing to enroll into the program and comply with program requirements.

The completed form is sent to the Nplate™ NEXUS Program for enrollment. The Nplate™ NEXUS Program will screen the patient identifying information for previous enrollment in the Nplate™ NEXUS Program. A new patient enrollee will receive a unique Nplate™ NEXUS Program ID number; while a previously enrolled patient is linked to and will receive the Nplate™ NEXUS Program ID number previously assigned to them.

The Nplate™ NEXUS Program will review the form for completeness and check that the treating HCP is enrolled in the program. Non-enrolled HCPs will be required to enroll by completing an Nplate™ NEXUS Program Healthcare Provider Enrollment Form.

1.4 Ordering

Once the enrollment process is complete, an HCP or Institution can order Nplate™ through its preferred wholesaler following the standard ordering procedure for an injectable. Nplate™ will not be stocked with wholesalers. Wholesalers will be instructed to forward the order to the Nplate™ NEXUS Program. An HCP or Institution can also order Nplate™ by contacting the Nplate™ NEXUS Program directly.

In an enrolled Institution, a designated hospital staff member in the central pharmacy will check against a secure online database (or via telephone) whether the patient and the physician are enrolled in program before placing the order.

The number of patients enrolled by a specific HCP and the number of vials being shipped to the office will be maintained in the Nplate™ NEXUS Program database for auditing purposes.

1.5 Fulfillment

Nplate™ will only be distributed by one specialty distributor that is part of the Nplate™ NEXUS Program. Inventory of the specialty distributor will be replenished directly by Amgen.

On receipt of the Nplate™ order forwarded by a wholesaler, the specialty distributor will check:

- That the requesting HCP or Institution is enrolled in the program.
- That there are actively enrolled patients treated by the HCP or Institution.

On confirmation, the specialty distributor will ship Nplate™ to the HCP or institution. If one or more of the conditions is not met, the specialty distributor will contact the HCP and wholesaler to investigate and resolve the order.

HCPs and institutions will be allowed to return unused vials of Nplate™. Unused drug will be returned following Amgen's existing policy and procedures for drug returns. When a patient discontinues use of Nplate™ the product will be accepted for return from the physician for full credit.

Steps for returning product:

- HCP contacts Nplate™ NEXUS Program with identification for the patient that discontinued. This contact will also initiate the patient discontinuation process and completion of the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form by the Nplate™ NEXUS Program.
- The Nplate™ NEXUS Program processes a return material authorization (RMA) and arranges for product pick-up.
- The Nplate™ NEXUS Program receives, verifies and processes return.
- The Nplate™ NEXUS Program issues credit.

The Nplate™ NEXUS Program will conduct audits of shipments to assure program compliance.

The HCPs or Institutions not compliant will be dis-enrolled.

1.6 Hospital/ Institution Dispensing and Recordkeeping

For an Institution, a designated staff member will check against a secure online database (once available) or via telephone that both the prescribing HCP and the patient are enrolled in the Nplate™ NEXUS Program prior to dispensing Nplate™ for inpatient or outpatient use.

Enrolled institutions will be required to maintain drug accountability and reconciliation records to confirm that every prescription of Nplate™ received is from an enrolled HCP and for an enrolled patient, and to ensure detection of noncompliance. Product tracking includes the following information:

- Name and unique identification number of the enrolled prescribing healthcare provider
- Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate
- Date of each Nplate order (including number of vials ordered and vial sizes)
- Number of Nplate vials, vial sizes, and date of each dose given to each patient.
- Overall inventory for the set period of time including the total number of vials ordered (including vial sizes), dispensed, and in stock.

To assist institutions with recordkeeping, Amgen will make available a record template (hard copy and electronic); institutions may choose to use their own drug accountability and reconciliation records as long as all the required elements are captured. Amgen will conduct periodic audits to assure program compliance and will dis-enroll institutions for noncompliance.

1.7 Treatment Continuation

The HCP and Institution reordering process is the same ordering process described above.

The Nplate™ NEXUS Program will assist in the transition of an enrolled patient from inpatient to outpatient care. Inpatients that are enrolled in the Nplate™ NEXUS Program will be tracked through the Nplate™ NEXUS Program Patient Baseline Data Form. As part of the form, the inpatient HCP will fill in the name of the patient's outpatient HCP. The Nplate™ NEXUS Program will contact the outpatient HCP to fill in any missing data on the Nplate™ NEXUS Program Patient Baseline Data Form and continue to monitor the safety of the patient according to the Nplate™ NEXUS Program with the outpatient physician after the patient is discharged from the hospital. If the outpatient HCP is not currently enrolled in the Nplate™ NEXUS Program, assistance will be available for program enrollment. In addition, the Institution will develop a system to ensure patients started on Nplate™ as an inpatient are transitioned to an outpatient healthcare provider that is enrolled (or will be enrolled) in the Nplate™ NEXUS Program. Patients enrolling into the Nplate™ NEXUS Program attest by signing the Nplate™ NEXUS Program Patient Enrollment Form that "If I receive Nplate™ in the hospital, I understand that, upon discharge, I should immediately follow up with a healthcare provider to determine if continued Nplate™ treatment is appropriate." This guidance is also provided to patients in the Patient ID Card and Dosing Tracker and Nplate™ NEXUS Program Brochure.

Patients and HCPs will be encouraged to contact the Nplate™ NEXUS Program if a change in HCP occurs for an enrolled patient. As part of the safety monitoring, the Nplate™ NEXUS Program will also check patient rosters for each HCP and investigate any changes. On change of HCP, the Nplate™ NEXUS Program will check the enrollment status of the new HCP and assist with program enrollment if the new HCP is not enrolled.

1.8 Treatment Discontinuation

Treatment discontinuation can be initiated by the prescriber and/or the patient. Prescribers are required to notify the Nplate™ NEXUS Program if there is a discontinuation of therapy. In addition, the Nplate™ NEXUS Program call center will become aware of a patient discontinuation through monitoring of monthly orders, and/or contact with the prescriber when completing the Nplate™ NEXUS Program Safety Questionnaire. When notified of a discontinuation of therapy, the Nplate™ NEXUS Program will request the reason for therapy discontinuation and follow-up with additional safety questions as appropriate. Follow-up will include inquiry on specific solicited risks associated with Nplate™. The HCP will be prompted to complete the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form upon patient discontinuation, and no later than 6 months after discontinuation. Amgen Global Safety will coordinate additional investigation based on Amgen standard procedures on discontinuations due to adverse events or loss of efficacy.

The Nplate™ NEXUS Program will attempt 3 contacts (two fax and one telephone contact) within a 6-month period if the healthcare professional does not complete the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form within the ascribed 6-month period. If the Nplate™ NEXUS Program is not able to obtain the necessary response, the patient will be sent one certified letter requesting information regarding the discontinuing of Nplate™. If the HCP fails to comply with program requirements, dis-enrollment procedures will be initiated.

Following discontinuation of treatment, an HCP may decide to restart a patient on Nplate™. Upon restarting treatment, patients will “re-enroll” by signing an Nplate™ NEXUS Program Patient Enrollment Form following the same process for new patients. To ensure continuity of records, the re-enrolling patient will be reassigned their original Nplate™ NEXUS ID number.

1.9 Safety Stock

Enrolled HCPs will have the option to carry a safety stock of 2 vials of Nplate™. Enrolled hospitals will have the option to carry a safety stock of 10 vials. The safety stock is a small quantity of Nplate™ and can only be used for enrolled patients; therefore, Amgen does not anticipate inappropriate use and/or additional safety concerns. A summary of the procedure for ordering and replenishing a safety stock of Nplate™ is as follows:

- The enrolled HCP (or designated hospital person) will order safety stock directly from the Nplate™ NEXUS Program.
- The Nplate™ NEXUS Program will flag the request so that no additional safety stock can be shipped beyond the limit of 2 vials (for an HCP) or 10 vials (for a hospital).
- The HCP will enroll a patient following the regular procedure. Because the patient will receive doses from the safety stock, the HCP will also specify the number of vials (1 or 2) that will be administered to the patient.
- The Nplate™ NEXUS Program will process the request for Nplate™ similarly to the regular process; the Nplate™ NEXUS Program will also authorize a shipment to replenish the safety stock.

In case of emergency an HCP may contact the Nplate™ NEXUS Program directly and request an emergency shipment. Nplate™ will be shipped within 24 hours whereby the HCP and patient will then be enrolled to the Nplate™ NEXUS Program. The Nplate™ NEXUS Program will follow up with the HCP to enroll to the program and request the HCP to enroll the patient into the Program.

Nplate™ (romiplostim) NEXUS Program Institution Enrollment Form

I understand that Nplate™ (romiplostim) is only available through the Nplate™ NEXUS Program (the "Program"). A healthcare professional must be enrolled in the Nplate™ NEXUS Program to prescribe Nplate™. Patients must be enrolled in the Nplate™ NEXUS Program to receive Nplate™. Nplate™ will be distributed to enrolled hospitals/institutions via a drop ship program through which Amgen retains direct control over these Nplate™ purchases. Enrolled hospitals/institutions may order Nplate™ through their usual distributor or through the Nplate™ NEXUS Program directly, whichever they prefer. If ordered through the distributor, the distributor will transmit the order to the Nplate™ NEXUS Program for drop shipment. I agree to comply with the following Program requirements on behalf of my institution:

- Develop a system, order sets, protocols, or other measures to ensure that Nplate™ is only dispensed to inpatients and outpatients (eg, in a clinic) after verifying that the prescribing healthcare provider and patient are enrolled in the Nplate™ NEXUS Program;
- Train and provide educational materials to appropriate staff responsible for prescribing, dispensing, and administering Nplate™ regarding the safe and appropriate use of Nplate™, program monitoring requirements (including dispensing a Medication Guide with each dose), program adverse event reporting requirements, and institution documentation requirements;
- To develop a system to ensure patients started on Nplate™ as inpatients are transitioned to an outpatient healthcare provider who is enrolled (or will be enrolled) in the Nplate™ NEXUS Program; and
- To develop a process and system to track Nplate™ NEXUS Program compliance and cooperate with periodic audits to assure that Nplate™ is used in accordance with the program requirements. Product tracking includes the following information:
  - Name and unique identification number of the enrolled prescribing healthcare provider
  - Unique identifier (program ID number, name, date of birth, address) of the enrolled patient receiving Nplate™
  - Date of each Nplate™ order (including number of vials ordered and vial sizes)
  - Number of Nplate™ vials, vial sizes, and date of each dose given to each patient
  - Overall inventory for the set period of time including the total number of vials ordered (including vial sizes), dispensed, and in stock

NEXUS Specialists and Amgen representatives are available as resources to healthcare providers to assist in Nplate™ NEXUS Program enrollment and Nplate™ training. An Nplate™ NEXUS Program Training Kit is available to inform prescribers of Nplate™ and the Nplate™ NEXUS Program. If you need additional kits, please specify the number needed below.

Please send an additional _____ Nplate™ NEXUS Program Training Kits.

Amgen will be regularly evaluating program compliance to ensure that program objectives are met. Amgen reserves the right to terminate an institution's enrollment at any time based upon the institution's noncompliance with program requirements, or take other appropriate measures to assure that program objectives are met.

Authorized Institution Signature _____ Date _____/_____/_____
MM DD YYYY

Authorized Institution Name (print)_____ Title _____

Institution Enrollment Information

Institution Name _____

Primary Ship-to Address _____

City, State, ZIP Code _____

HIN _____ DEA Number _____

Phone ( )_____–_____ Fax ( )_____–_____

(Institution Point of Contact) _____ Phone ( )_____–_____ Fax ( ) _____–_____

Please fax this completed form to the Nplate™ NEXUS Program at 1-877-675-2830.
A NEXUS Specialist will follow up to obtain information for communication, shipping, and ordering.
You will receive enrollment confirmation via fax within 48 hours.
For questions regarding the Nplate™ NEXUS Program, call 1-877-NPLATE1 (1-877-675-2831).

Nplate™ (romiplostim) Nexus

Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

Nplate™ (romiplostim)
REMS
PROCEDURES FOR DIRECT SHIPMENT TO REGISTERED HEALTHCARE PROVIDERS AND HOSPITALS/INSTITUTIONS

Objective
To describe the procedure utilized to restrict distribution of Nplate™ (romiplostim) to healthcare providers and hospitals/institutions that are enrolled in the Nplate™ NEXUS Program.

Action
- The Nplate™ NEXUS Program maintains and updates a list of enrolled healthcare providers and hospitals/institutions to receive and dispense Nplate™.
- Amgen ships Nplate only to the central distribution center which is part of the Nplate™ NEXUS Program.
- Through the Nplate™ NEXUS Program, the central distribution center will only ship Nplate to enrolled healthcare providers and hospital/institutions treating enrolled patients.
- Healthcare providers and hospitals/institutions place orders for Nplate through their normal procurement channels (i.e., wholesalers) or directly through the Nplate™ NEXUS Program.
- Wholesalers transmit orders made by healthcare providers and hospital/institution orders to the Nplate™ NEXUS Program either electronically or manually.
- Wholesalers, except the Nplate™ NEXUS Program central distribution center, are not eligible to carry inventory of or distribute Nplate.
- The Nplate™ NEXUS Program central distribution center receives the order either from the wholesaler, healthcare provider, or hospital/institution directly and verifies that the healthcare provider or hospital/institution is treating enrolled patients.
    - Once enrollment is verified, Nplate is shipped directly to the healthcare provider's office or hospital/institution
    - If enrollment cannot be verified, the customer is contacted by the Nplate™ NEXUS Program specialist to assist with enrollment
- Orders are shipped from the Nplate™ NEXUS Program as follows:
    - The number of vials ordered are packed in an appropriate cold shipping container, addressed to enrolled healthcare provider's or hospital's/institution's name and address
    - The shipping container is sealed and staged to the outbound staging area for pick up by an authorized delivery service for delivery per customer request.
- Via the invoice, the Nplate™ NEXUS Program notifies the customer's designated wholesaler through which the order was placed, that the shipment to the enrolled healthcare provider or hospital/institution has been made.

Nplate™ (romiplostim) NEXUS Program Patient Enrollment Form

Patient Information

Patient Name_____

Gender: Female ☐ Male ☐ Date of Birth (MM/DD/YY) _____

Mailing Address_____

City, State, ZIP_____ Phone (____) _____ - _____

E-mail (optional)_____ Is Nplate™ being initiated in the inpatient setting? ☐ Yes ☐ No

Healthcare Provider Information:

Treating Healthcare Provider_____ NEXUS ID (optional)_____

Address_____

City_____ State_____ ZIP_____

Phone (____) _____ - _____ Fax (____) _____ - _____ E-mail_____

Patient Acknowledgment

- I have read and understand the Medication Guide for Nplate™ that my prescriber has given to me.
- I have asked and discussed any questions or concerns about Nplate™ or my treatment with my healthcare provider.
- I am aware that Nplate™ is associated with the following risks:
  - — Long-term use of Nplate™ may cause changes in my bone marrow. These changes may lead to abnormal blood cells or my body making less blood cells.
  - — When I stop receiving Nplate™, my low blood platelet count (thrombocytopenia) may become worse than before I started receiving Nplate™.
  - — I have a higher chance of getting a blood clot if my platelet count is too high during treatment with Nplate™.
  - — Nplate™ may worsen blood cancers. Nplate™ is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS).
- I will report any adverse events to my prescriber.
- I understand that I should not discontinue Nplate™ without talking to my healthcare provider.
- If I receive Nplate™ in the hospital, I understand that, upon discharge, I should immediately follow up with a healthcare provider to determine if continued Nplate™ treatment is appropriate.
- I understand that I should always carry my Patient ID Card and Dosing Tracker.

Patient Acknowledgment (cont'd)

- I must notify the Nplate™ NEXUS Program if I switch to a different healthcare provider for Nplate™ treatment by calling 1-877-NPLATE1 (1-877-675-2831).
- I understand that in order to receive Nplate™, I will be automatically enrolled in the Nplate™ NEXUS Program. My healthcare provider will monitor how I am doing on Nplate™ and report to the Nplate™ NEXUS Program every 6 months about certain serious side effects, and to make sure Nplate™ is right for me.
- I understand that if I do not sign this Patient Acknowledgment, I will not be enrolled in the Nplate™ NEXUS Program and will not be able to receive Nplate™.

_____ ____ / ____ /____

Patient Signature **Date (MM/DD/YY)**

Patient Authorization for Disclosure and Use of Health Information

I hereby authorize each of my physicians, pharmacists, and other healthcare providers (together, my "**Providers**") and each of my health insurers (together, my "**Insurers**") to disclose my personally identifiable health information, including information related to my medical diagnosis, condition, and treatment (including lab and prescription information), my health insurance, and my name, address, and telephone number (together, my "**Health Information**") to Amgen Inc., its agents and representatives, including third parties authorized by Amgen Inc. to administer the Nplate™ NEXUS Program (together, "**Amgen**") for the purposes described below.

Specifically, I authorize Amgen to receive, use, and disclose my Health Information in order to:

(i) enroll me in the Nplate™ NEXUS Program and administer my participation (including contacting me) in the Nplate™ NEXUS Program;

(ii) interact with my Providers regarding shipment and receipt of Nplate™ and regarding direct drug shipment to the appropriate site;

(iii) evaluate the safety of Nplate™ and the effectiveness of the Nplate™ NEXUS Program;

(iv) provide me with educational kits and other information with respect to the Nplate™ NEXUS Program and/or my medical condition;

(v) contact my Providers to collect, enter, and maintain my Health Information in a database;

(vi) make submissions to government agencies and other authorities, including, but not limited to, the FDA, regarding matters such as adverse events and Nplate™ NEXUS Program effectiveness;

(vii) as relating to a diagnosis of ITP, verify my insurance coverage, review reimbursement issues, enroll me into appropriate assistance programs, and assist with the adjudication of claims, which activities may include interaction with my Insurers;

(viii) further use and disclose my Health Information as required or permitted by applicable law; and

(ix) de-identify my Health Information for use or disclosure as permitted by applicable law.

I understand that once my Health Information has been disclosed to Amgen, federal privacy laws may no longer protect the information and that my Health Information may be subject to re-disclosure. However, Amgen agrees to protect my information by using and disclosing it only for the purposes described.

I understand that I am not required to sign this Authorization. However, if I do not sign, I will not be able to enroll in the Nplate™ NEXUS Program to receive Nplate™ and may not receive the other services described above. Otherwise, however, my treatment, payment for treatment, insurance enrollment, or eligibility for insurance benefits, will not be directly affected by my decision not to sign this Authorization.

I understand that I may revoke (withdraw) this Authorization at any time by faxing a signed, written request to: The Nplate™ NEXUS Program, at 1-877-NPLATE0 (1-877-675-2830). Amgen shall notify my Providers and Insurers of my revocation,who may no longer disclose my Health Information to Amgen once they have received and processed that notice. However, revoking this Authorization will not affect Amgen's ability to use and disclose my Health Information that it has already received to the extent permitted under applicable law. If I revoke this Authorization, I will no longer be able to participate in the Nplate™ NEXUS Program to receive Nplate™ and may not receive the other services described above.

This Authorization expires ten (10) years from the date that I sign it.

I understand and agree with the terms and conditions of this three-page Authorization. I also understand that I have a right to receive a copy of this Authorization upon request.

_____ ____/____/____

Signature of Patient or Personal Representative **Date (MM/DD/YY)**

_____

Printed Name of Patient or Personal Representative

_____

Personal Representative's Relationship to Patient (if applicable)

Instructions

Upon completion, please fax a copy to the Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830).

Welcome to the Nplate™ (romiplostim) NEXUS Program.

Nplate™ is only available through the Nplate™ NEXUS (Network of EXperts Understanding and Supporting Nplate™ and patients) Program. This program is designed to inform you about the risks and benefits of using Nplate™. You and your healthcare provider will be able to discuss these risks and what this means for you. You will receive a Medication Guide as part of the program brochure which will describe the risks and benefits of using Nplate™.

The Nplate™ NEXUS Program includes a registry that requires all patients treated with Nplate™ to be enrolled. Part of the registry requires that your healthcare provider monitor how you are doing on Nplate™, to report to the Nplate™ NEXUS Program every 6 months about certain serious side effects, and to make sure Nplate™ is right for you.

Your healthcare provider will explain the content of the Nplate™ NEXUS Program Patient Enrollment Form which you must sign before receiving the medicine. After you are enrolled, you can start Nplate™ treatment. Only a healthcare provider can give you Nplate™ by an injection under your skin.

The Nplate™ NEXUS Program also provides additional educational material including:

- "What is Nplate™ NEXUS?"—a brochure for Nplate™ patients and caregivers, including the Medication Guide
- Patient ID Card and Dosing Tracker

What is Nplate™?

Nplate™ is a man-made protein medicine used to treat low blood platelet counts in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), when other medicine to treat your ITP is not the best choice for you or surgery to remove the spleen has not worked well enough.

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

Nplate™ can cause uncommon but serious side effects:

- **Bone marrow changes (increased reticulin and possible bone marrow fibrosis).** Long-term use of Nplate™ may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called "increased reticulin." It is not known if this may progress to a more severe form called "fibrosis." The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormalities in your blood tests. Your healthcare provider will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate™.

- **Worsening low blood platelet count (thrombocytopenia) and risk of bleeding shortly after stopping Nplate™.** When you stop receiving Nplate™, your low blood platelet count (thrombocytopenia) may become worse than before you started receiving Nplate™. These effects are most likely to happen shortly after stopping Nplate™ and may last about 2 weeks. The lower platelet counts during this time period may increase your risk of bleeding, especially if you are taking a blood thinner or other medicine that affects platelets. Your healthcare provider will check your blood platelet counts for at least two weeks after you stop taking Nplate™. Call your healthcare provider right away to report any bruising or bleeding.

- **High platelet counts and higher chance for blood clots.** You have a higher chance of getting a blood clot if your platelet count is too 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. Your healthcare provider will check your blood platelet counts and change your dose or stop Nplate™ if your platelet counts get too high.

- **Worsening of blood cancers.** Nplate™ is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). If you have one of these conditions, Nplate™ may worsen your cancer or condition and may cause you to die sooner.

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™ are:

- Headache
- Joint pain
- Dizziness
- Trouble sleeping
- Muscle tenderness or weakness
- Pain in arms and legs
- Abdominal pain
- Shoulder pain
- Indigestion
- Tingling or numbness in hands and feet

These are not all the possible side effects of Nplate™. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. For more information, ask your healthcare provider or pharmacist.

If you have any questions about this information, be sure to discuss them with your doctor. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. You may also report side effects to the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831).

Please visit www.nplate.com for more information.

At Amgen, our mission is to serve patients. We are honored to be of service to you.

Thank you,
The Nplate™ NEXUS team

Nplate™(romiplostim)

Nexus

Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

What is Nplate™ NEXUS?

A brochure for Nplate™ patients and caregivers,
including the Medication Guide

Connecting with Nplate™ (romiplostim) therapy: The steps of the Nplate™ NEXUS Program

1 Enroll

- Your healthcare provider will explain to you what Nplate™ is, and how it is used.
- Your healthcare provider will explain the risks and benefits of using Nplate™ and give you the Nplate™ Medication Guide.
- You and your healthcare provider will fill out and sign forms once you understand Nplate™ and its benefits and risks. You will also be asked to sign a form authorizing the Nplate™ NEXUS Program to ask your healthcare provider some specific questions about how you are tolerating Nplate™ therapy.

Nplate™ (romiplostim) Nexus

1-877-NPLATE1 (1-877-675-2831)

2 Reimbursement Assistance (optional)

- As you enroll in the Nplate™ (romiplostim) NEXUS Program, you may request insurance or payment assistance. Insurance specialists at the Nplate™ NEXUS Program will work with you and look for assistance programs for which you might be eligible.
- You can call the Nplate™ NEXUS Program at any time to answer any of your questions about insurance or financial assistance options by calling 1-877-NPLATE1 (1-877-675-2831).

3 Receiving Nplate™ Treatment

- Upon enrollment, a NEXUS Specialist arranges shipment of Nplate™ to your healthcare provider's office.
- Your healthcare provider must administer the Nplate™ injections in his/her office for you.
- Your healthcare provider will monitor how you are doing on Nplate™ and report any serious side effects to the Nplate™ NEXUS Program. Therefore, the Nplate™ NEXUS Program Patient Enrollment Form asks your permission to allow NEXUS Specialists to speak to your healthcare provider about any side effects that you might have experienced during, and after, therapy.
- If you receive Nplate™ in the hospital, upon discharge, you should immediately follow up with a healthcare provider to determine if continued Nplate™ treatment is appropriate.

If you have any questions or concerns, please speak to your healthcare provider or to a NEXUS Specialist.

4 Support and Follow-up

- NEXUS Specialists are available to answer any questions about Nplate™ therapy, support programs, or insurance issues.
- Upon enrollment, you will receive, from your healthcare provider, an education kit about the Nplate™ NEXUS Program.

Nplate™ (romiplostim) Nexus

Network of EXperts | Understanding and Supporting Nplate™ (romiplostim) and patients

MEDICATION GUIDE

Nplate™
(romiplostim)

Read this Medication Guide before you start Nplate™ and before each Nplate™ injection. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Nplate™ can cause uncommon but serious side effects:

- **Bone marrow changes (increased reticulin and possible bone marrow fibrosis).** Long-term use of Nplate™ may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called "increased reticulin." It is not known if this may progress to a more severe form called "fibrosis." The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormalities in your blood tests. Your healthcare provider will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate™.

MEDICATION GUIDE (cont'd)

- **Worsening low blood platelet count (thrombocytopenia) and risk of bleeding shortly after stopping Nplate™.** When you stop receiving Nplate™, your low blood platelet count (thrombocytopenia) may become worse than before you started receiving Nplate™. These effects are most likely to happen shortly after stopping Nplate™ and may last about 2 weeks. The lower platelet counts during this time period may increase your risk of bleeding, especially if you are taking a blood thinner or other medicine that affects platelets. Your healthcare provider will check your blood platelet counts for at least two weeks after you stop taking Nplate™. Call your healthcare provider right away to report any bruising or bleeding.

- **High platelet counts and higher chance for blood clots.** You have a higher chance of getting a blood clot if your platelet count is too 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. Your healthcare provider will check your blood platelet counts and change your dose or stop Nplate™ if your platelet counts get too high.

- **Worsening of blood cancers.** Nplate™ is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). If you have one of these conditions, Nplate™ may worsen your cancer or condition and may cause you to die sooner.

When you are being treated with Nplate™, your healthcare provider will closely monitor your Nplate™ dose and blood tests, including platelet counts.

MEDICATION GUIDE (cont'd)

- Nplate™ is available only after you and your healthcare provider agree to join a program that is intended to help in the safe use of Nplate™. This program is called the "Nplate™ NEXUS Program."
- Only a healthcare provider can inject a dose of Nplate™. Injection of too much Nplate™ may cause a dangerous increase in your blood platelet count and serious side effects.
- During Nplate™ therapy, your healthcare provider may change your Nplate™ dose, depending upon the change in your blood platelet count. You must have blood platelet counts done before you start Nplate™, during Nplate™ therapy, and after Nplate™ therapy is stopped.
- 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.

See "**What are the possible side effects of Nplate™?**" for other side effects of Nplate™.

What is Nplate™?

Nplate™ is a man-made protein medicine used to treat low blood platelet counts in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), when other medicine to treat your ITP is not the best choice for you or surgery to remove the spleen has not worked well enough.

Nplate™ is only:

- Prescribed by healthcare providers who are enrolled in the Nplate™ NEXUS Program.
- Given to patients who are enrolled in the Nplate™ NEXUS Program.
- Given by the enrolled healthcare provider or a provider under their direction. You may not give Nplate™ injections to yourself.

It is not known if Nplate™ works or if it is safe in people under the age of 18.

Nplate™ is for treatment of certain people with low blood platelet counts caused by chronic ITP, not low platelet counts caused by other conditions or diseases.

What should I tell my doctor before taking Nplate™?

Tell your doctor about all 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 bleeding problems
- Are pregnant, think you may be pregnant, or plan to get pregnant. It is not known if Nplate™ will harm an unborn baby.

***Pregnancy Registry*:** There is a registry for women who become pregnant during treatment with Nplate™. If you become pregnant, consider this registry. The purpose of the registry is to collect safety information about the health of you and your baby. Contact the registry as soon as you become aware of the pregnancy, or ask your healthcare provider to contact the registry for you. You or your healthcare provider can get information and enroll in the registry by calling 1-877-NPLATE1 (1-877-675-2831).

- Are breast-feeding or plan to breast-feed. It is not known if Nplate™ passes into your breast milk. You and your healthcare provider should decide whether you will take Nplate™ or breast-feed. You should not do both.

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

How should I take Nplate™?

To receive Nplate™, you must first talk with your healthcare provider and understand the benefits and risks of Nplate™. You must agree to and follow all of the instructions in the Nplate™ NEXUS Program.

Before you can begin to receive Nplate™, your healthcare provider will:

- Explain the Nplate™ NEXUS Program to you
- Answer all of your questions about Nplate™ and the Nplate™ NEXUS Program
- Make sure you read the Nplate™ Medication Guide
- Have you sign the Nplate™ NEXUS Program Patient Enrollment Form

Nplate™ is given by your healthcare provider as a subcutaneous (SC) injection under the skin one time each week.

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 have 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 while you are receiving Nplate™.

If you miss a scheduled dose of Nplate™, call your healthcare provider to arrange for 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 arrange for your next dose as soon as possible. Call your doctor or the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831).

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™ are:

- Headache
- Joint pain
- Dizziness
- Trouble sleeping
- Muscle tenderness or weakness
- Pain in arms and legs
- Abdominal pain
- Shoulder pain
- Indigestion
- Tingling or numbness in hands and feet

These are not all the possible side effects of Nplate™. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. For more information, ask your healthcare provider or pharmacist.

MEDICATION GUIDE (cont'd)

Call your doctor for medical advice about side effects. You may report side effects to the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831) or FDA at 1-800-FDA-1088.

General information about the safe and effective use of Nplate™

This Medication Guide summarizes the most important information about Nplate™. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Nplate™ that is written for health professionals.

What are the ingredients in Nplate™?

Active ingredient: romiplostim

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

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.

www.nplate.com

1-877-NPLATE1 (1-877-675-2831)

3XXXXXX
v1 Issue Date: 08/2008

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

Nplate™(romiplostim)

Nexus

Network of EXperts Understanding and Supporting Nplate™ (romiplostim) and patients

Please fill in this information as you begin Nplate™(romiplostim) therapy.

Patient name

Weight in kg at start of therapy

Platelet count at start of therapy

Physician name

Physician phone number

Give this card to your healthcare provider every time you receive Nplate™ or get your platelet count checked.

DATE	DOSE (mcg/kg)

Nplate™ romiplostim

Keep track of important Nplate™ information by giving this card to your healthcare provider every time you receive Nplate™ or get your platelet count checked.

Patient ID Card and Dosing Tracker

Nplate™ is a man-made protein medicine used to treat low blood platelet counts in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), when other medicine to treat your ITP is not the best choice for you or surgery to remove the spleen has not worked well enough.

Nplate™ can cause uncommon but serious side effects: bone marrow changes, worsening low blood platelet count and risk of bleeding shortly after stopping Nplate™, high platelet counts and higher chance for blood clots, and worsening of blood cancers.

If you receive Nplate™ in the hospital, upon discharge, you should immediately follow up with a healthcare provider to determine if continued Nplate™ treatment is appropriate.

For more information about Nplate™, please see the accompanying prescribing information and medication guide or visit **www.nplate.com**.

You can call the Nplate™ NEXUS Program at 1-877-NPLATE1 (1-877-675-2831) for more information about Nplate™ therapy.

Patient ID Card and Dosing Tracker

Keep track of important Nplate™ information by giving this card to your healthcare provider every time you receive Nplate™ or get your platelet count checked.

Nplate™
romiplostim

Nplate™
romiplostim

For more information about Nplate™, please see the accompanying Prescribing Information and Medication Guide, or visit **www.nplate.com**.

Nplate™ (romiplostim)
REMS
Nplate™ NEXUS PATIENT SAFETY REGISTRY

All patients treated with Nplate™ will be enrolled in the Nplate™ NEXUS Patient Safety Registry (PSR) to collect information regarding their demographics, baseline status, treatment, and adverse events.

The objective is to gather, maintain, assess, and report solicited pre-defined serious adverse events (SAEs) associated with the use of Nplate™.

In addition the registry will encourage the usual spontaneous adverse event reporting for events apart from the solicited SAEs.

Primary objective:

- To calculate the incidence of predefined serious adverse events (SAEs) associated with risks of Nplate™ that resulted in a serious outcome in patients receiving Nplate™.

Secondary objectives:

- To calculate the incidence of all other SAEs and non-serious AEs among all patients who receive Nplate™ therapy.
- To calculate the incidence of Nplate™ discontinuation due to occurrence of an AE.
- To determine whether Nplate™ treatment should be continued for another 6 months.

Key elements of the Nplate™ NEXUS Patient Safety Registry include:

- All patients enrolled in the Nplate™ NEXUS Program are included in the Patient Safety Registry
- All available patient baseline demographic and disease characteristics will be captured and entered into the registry for all enrolled patients
- HCPs will be encouraged at all contacts to report adverse events in real time by contacting the Nplate™ NEXUS Program call center. All reported SAEs will be followed up by Amgen Global Safety (AGS) for completeness and outcome.
- At 6 month intervals, the NEXUS Specialists will ask the HCP if any predefined SAE associated with Nplate™ risks was observed in their patient(s) receiving Nplate™ therapy and whether Nplate™ treatment should be reauthorized using the Nplate™ NEXUS Safety Questionnaire. The predefined risk of worsened thrombocytopenia after cessation of treatment will be captured in the Patient Discontinuation/Post Discontinuation Follow-Up Form and in the Worsened Thrombocytopenia after Cessation of Treatment with Nplate™ Form. If a predefined SAE was observed, the NEXUS Specialist will ask if it has been reported to the Nplate™ NEXUS call center. If it has not, the NEXUS Specialist will facilitate the intake of the event using specific pre-defined form for each risk.
    - The NEXUS Specialist will also ask the HCP if any other not predefined SAE was observed and if it was previously reported by the HCP to the Nplate™

NEXUS call center. If it was not, the NEXUS Specialist will facilitate the intake of the SAE.

- Patient discontinuation due to an AE will be captured in the registry. If discontinuation is attributed to a predefined SAE, AGS will conduct standard follow-up including capturing relevant details in Amgen's safety database.

The aggregate data collected in the PSR will be reviewed at least semi-annually.

Patient Safety Registry Design

The PSR is a single arm registry of all patients receiving Nplate™ therapy in the US. Nplate™-treated patients will be enrolled and followed-up in the PSR through their prescribing HCPs.

Collection of Baseline Patient Demographic Information

All patients receiving Nplate™ will be enrolled in the Nplate™ NEXUS Program. At that time, patients will be entered into the PSR by the submission of basic demographic information (name, date-of-birth, and gender) to the Nplate™ NEXUS Program call center using the Nplate™ NEXUS Patient Program Enrollment Form. The HCP will be requested to provide all additional available baseline data at the time of enrollment or within 30 days of the patient enrollment using the Nplate™ NEXUS Patient Baseline Data Form.

The HCP or HCP representative will be prompted three times within the first 30 days of patient enrollment to provide any additional available patient baseline data. This data can be provided directly to the NEXUS Specialist via a telephone interview or by completing the Nplate™ NEXUS Patient Baseline Data Collection Form online. This data will be collected for each patient to the extent the information is available. If the baseline data received is not complete, the Nplate™ NEXUS Program has standard operating procedures for collecting missing information as listed below:

- An email or a fax (based on site's preference) is sent to the site at Day 5
- If the baseline data is still not completed by Day 15, a telephone call is made to the site
- If the baseline data is still not completed by Day 30, an email or fax (based on site's preference) is sent to the site on Day 30
  - Contact attempts will be logged with each attempt on Days 5, 15, and 30
- If the baseline data is still not completed after Day 30, then Amgen contacts the site, and the dis-enrollment process is considered
- Certified letter is sent to the HCP informing on a pending dis-enrollment and remediation procedures.

- If no response after 14 days of the receipt of the certified letter, dis-enrollment procedures begin

Consent to provide this information to the sponsor is given in both the Nplate™ NEXUS Healthcare Provider Enrollment Form and in the Nplate™ NEXUS Patient Program Enrollment Form. Provision of the data will not be used as criteria for inclusion or exclusion into the Nplate™ NEXUS Program, nor will it be used for the evaluation of patient diagnosis or treatment. The data will serve as a basis for comprehensive assessment of the predefined SAEs as well as for statistical analysis. These data will be utilized as aggregate data in Nplate™ safety analyses.

Table 1. Description of Baseline Characteristics for All Patients Using Nplate™

Data obtained at initial patient enrollment in Nplate™ NEXUS Program:	**Additional data obtained within 30-days of patient enrollment in the Nplate™ NEXUS Program:**
Patient name Gender Birth date	Race (optional) Duration of ITP or disease for which Nplate™ is prescribed Pre-treatment platelet count (prior to romiplostim) Previous therapies (for ITP or for disease for which Nplate™ is prescribed) Splenectomy status Results of any previous bone marrow biopsy, if available Previous history of bone marrow abnormalities Concomitant medication use for ITP or for disease for which Nplate™ is prescribed Preexisting comorbid conditions at baseline (ie, TE events, neoplasms)

Collection of Adverse Events

Enrolled HCPs will be educated on the purpose and objectives of the PSR. They will also be educated on the romiplostim risks and instructed to report adverse events to the Nplate™ NEXUS Program call center. Healthcare providers will be encouraged to report all adverse events in real time. All reported predefined and not predefined SAEs will be followed up by Amgen for completeness and outcome. All predefined SAEs and suspected unexpected serious adverse reactions (SUSARs) will be deemed related to Nplate™ treatment by default and reported to the agency in an expedited manner as 15 day reports.

In addition, the treating HCP will be prompted and reminded every 6 months to complete the Nplate™ NEXUS Safety Questionnaire for each patient receiving Nplate™. The 6-month review cycle will be HCP-based and determined at the time of HCP enrollment; all newly enrolled patients will be entered into their respective HCP's 6-month review cycle. The purpose of these communications are to 1) remind the HCP of the importance of reporting adverse events observed in patients receiving Nplate™, 2) ask if the HCP observed and reported any SAEs in their patient receiving Nplate™, 3) facilitate the intake of any non-reported SAE, and 4) ask the HCP if Nplate™ treatment should be continued/reauthorized for the next 6 months.

Reported cases of SAEs will be followed by Amgen using the processes established for intake of spontaneous serious adverse event reporting as noted in Amgen Standard Operating Procedure. The Amgen safety database will be the repository of all AE reports received.

SAE reports will be sent to Regulatory Agencies in an expedited manner per local regulatory requirements.

Patients enrolled into the Nplate™ NEXUS Program who experience an AE will be able to report the AE directly to the Nplate™ NEXUS Program call center. The AE reported by the patient will be triaged in the Nplate™ NEXUS Program call center and entered into the Amgen safety database as a spontaneous consumer report.

All serious, medically confirmed AEs will be reported in the Periodic Safety Update Report (PSUR) to FDA. All reported adverse events included in the PSR will be searchable in the Amgen safety database for analysis as needed, by event or by patient. These data will be analyzed, tabulated, and distributed internally every 6 months and whenever needed.

Re-assessment of risks will be based on drug exposure which is dependent upon frequency of events and patient enrollment into the program.

An independent External (non-Amgen) Advisory Panel will be established to provide an objective assessment of the predefined SAE data; the Panel will be scheduled to meet semi-annually.

Patient Lost to Follow-up

If during the 6-month Nplate™ NEXUS Safety Questionnaire call, a patient is reported by the HCP as 'lost to follow-up', the NEXUS Specialist will attempt to contact the patient via one certified letter. If the patient is reached and has switched to a different HCP, the NEXUS Specialist will check against the HCP database and verify if the current HCP is enrolled in the program. If the patient indicates that treatment has been discontinued, the NEXUS Specialist will inactivate the patient from the database and close the file. If applicable, Amgen will inquire whether the patient discontinued Nplate™ due to an adverse event and will collect the safety information according to the procedures highlighted in the Nplate™ NEXUS Patient Safety Registry.

Nplate™ (romiplostim) NEXUS Program Patient Baseline Data Form

1. Patient Information

Initials: _____	☐ Male ☐ Female	Race	**Upon initiation of Nplate™ therapy, is this patient:** ☐ Inpatient ☐ Outpatient
ICD-9 Code: _____	Diagnosis: _____	☐ Caucasian ☐ Asian ☐ Hispanic	If inpatient, referring physician: _____
Nplate™ NEXUS Patient ID#: _____	Date of Birth: ___ /___ / _____ (MM/DD/YYYY)	☐ African American ☐Other: _____	Telephone Number: _____

2. Patient ITP Information

Nplate™ Start Date in NEXUS: ___ /___ / _____ (MM/DD/YY)	Previous Treatment with Nplate™ prior to enrollment: ☐ Yes ☐ No
	If Yes, From: ___ /___ / _____ (MM/DD/YY) To: ___ /___ / _____ (MM/DD/YY)
Baseline Platelet Count Prior to Initiation of Nplate Therapy : _____ (x 10^9/L)	
Splenectomy ☐ Yes ☐ No	If known, when: ___ /___ / _____ (MM/DD/YY)

Date ITP Was First Diagnosed

_____/____/____ (MM//DD/YY)

☐ Unknown

Previous ITP Therapies

			Start Date (MM/DD/YY)	Stop Date (MM/DD/YY)
Corticosteroids:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
IVIg:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Danazol:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Rituximab:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Interferon alpha:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Azathioprine:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Cyclophosphamide:	☐ Yes	☐ No	___ /___ / _____	___ /___ / _____
Other: _____			___ /___ / _____	___ /___ / _____
Other: _____			___ /___ / _____	___ /___ / _____

Unknown: ☐

Current ITP therapies ☐ No ☐ Yes, select one or more of the following:

☐ Corticosteroids ☐ IVIg ☐ Danazol
☐ Rituximab ☐ Interferon alpha ☐ Azathioprine
☐ Cyclophosphamide Other: _____

Previous Bone Marrow Biopsy Results (Attach report) ☐ Yes ☐ Yes, not available ☐ No ☐ Unknown

Previous History of Bone Marrow Abnormalities ☐ None ☐ Yes, select one or more of the following:

☐ AML ☐ ALL ☐ CML ☐ Hodgkin's Disease ☐ Multiple Myeloma ☐ Aplastic Anemia
☐ MDS ☐ PNH ☐ NHL ☐ Myeloproliferative Disorders ☐ Amyloidosis ☐ Chronic Idiopathic Myelofibrosis
☐ Other, specify _____

3. Reporter Information

	Reporter Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ **Signature**
☐ Institution			

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

Nplate™ (romiplostim) NEXUS Program Safety Questionnaire

1. Patient Information

Initials: _____	NEXUS Program ID: _____ ☐ Male ☐ Female	ICD-9 Code: _____	Date of Birth: ___ /___ / _____ (MM/DD/YY) Diagnosis:

Is the patient still under your care? ☐ Yes ☐ No

If NO, please provide contact information for the new physician, if available: _____

Do you authorize the continuation of Nplate™ treatment for the next 6 months? ☐ Yes ☐ No

2. Nplate™ Treatment /Discontinuation Information

Is the patient currently receiving Nplate™? If yes, go to section 3 ☐ Yes ☐ No	If "No", Stop Date: ___ /___ / _____ (MM/DD/YY)	If "No", Last Dose Administered: _____ µg/kg	If "No", Platelet Count Upon Discontinuation: _____(x10^9/L)

If "No, Reason for Discontinuation		
	☐ Loss of response	☐ Adverse event (specify): _____
	☐ Lack of response	☐ Death: Cause of Death: _____ Date Deceased: ___ / ___ / ___ (MM/DD/YY)
	☐ Lost to follow-up	☐ Other (specify): _____

3. Safety Information

In the past 6 months, has the patient experienced any of the following Serious Adverse Events[1] not already reported to AMGEN?

Thrombosis or thromboembolism	☐ Yes ☐ No	☐Under Investigation
Hematological malignancy	☐ Yes ☐ No	☐Under Investigation
MDS	☐ Yes ☐ No	☐Under Investigation
Medication error associated with serious outcome	☐ Yes ☐ No	☐Under Investigation
Bone marrow reticulin	☐ Yes ☐ No	☐Under Investigation
Bone marrow fibrosis	☐ Yes ☐ No	☐Under Investigation

4. Additional Serious Adverse Events?

Has the patient experienced any additional serious adverse events in the past 6 months? ☐ Yes ☐ No

If Yes, specify: _____

Was the incident reported to AMGEN? ☐ Yes ☐ No

5. Reporter Information

	Reporter Name/Title (Print)	NEXUS program ID # (found on enrollment confirmation fax)	Date of report: ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ Signature
☐ Institution			

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

1 An adverse event is SERIOUS (SAE) when the patient outcome is: 1) Death – 2) Life threatening – 3) Hospitalization – initial or prolonged – 4) Significant disability/incapacity 5) Congenital anomaly/birth defect - 6) Other (important medical events)

Nplate™ (romiplostim) NEXUS Program: Patient Discontinuation/Post-Discontinuation Follow-Up

1. Patient Information

Initials: _____	NEXUS Program ID: _____ ☐ Male ☐ Female	ICD-9 Code: _____	Date of Birth: ___ /___ / _____ (MM/DD/YY) Diagnosis:

Is the patient still under your care? ☐ Yes ☐ No

If NO, please provide contact information for the new physician, if available:

Name: _____ Telephone #: _____

2. Nplate™ Treatment Information

Start Date: ___/___/___ (MM/DD/YY)	Last Dose Received: _____ µg/kg
Stop Date: ___/___/___ (MM/DD/YY)	Platelet Count Upon Discontinuation: ____ (x 10^9/L)

Reason for Discontinuation:	☐ Loss of response	☐ Adverse event (specify): _____
	☐ Lack of response	☐ Death: Cause of Death: _____ Date Deceased: ___/___/___ (MM/DD/YY)
	☐ Lost to follow-up	☐ Other (specify): _____

3. Safety Information

Was the discontinuation of Nplate™ observed with any of the following adverse events?

Worsening of thrombocytopenia after stopping Nplate™	□ Yes □ No □Under Investigation Date of onset: _____(MM/DD/YY)
Thrombosis or thromboembolism	□ Yes □ No □Under Investigation Date of onset: _____(MM/DD/YY)
Hematological malignancy	□ Yes □ No □Under Investigation If Yes, then, describe:_____ □ Progression of Previously diagnosed disease □ New onset Date of diagnosis: _____(MM/DD/YY)
MDS	□ Yes □ No □Under Investigation If Yes, then, □ Progression of Previously diagnosed disease □ New onset Date of diagnosis: _____(MM/DD/YY)
Nplate™ medication errors associated with serious outcomes	□ Yes □ No □Under Investigation Date of onset: _____(MM/DD/YY)
Bone marrow reticulin formation	□ Yes □ No □Under Investigation Date of onset: _____(MM/DD/YY)

Bone marrow fibrosis	□ Yes □ No □Under Investigation Date of onset: _____(MM/DD/YY)

4. Post-discontinuation Follow up

Since the report of discontinuation, has the condition: □ stabilized □ improved □ ongoing □ worsened □ resolved

If stabilized/improved/resolved: Date: ___/___/___ (MM/DD/YY)

5. Reporter Information

	Reporter Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			
☐ Institution			**Signature**

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

Nplate™ (romiplostim) NEXUS Program: Thrombotic/thromboembolic Complications

1. Patient Information

Initials: _____	NEXUS Program ID: _____	☐ Male ☐ Female	Date of Birth: ___ /___ / _____ (MM/DD/YY)

2. Nplate™ Administration Information

Nplate™ Start Date: ___ /___ / _____ (MM/DD/YY)	Nplate™ Stop Date: ___ /___ / _____ (MM/DD/YY) ☐ N/A[1]	Latest/last Dose Received: _____ µg/kg	Platelet Counts: Prior to initiation of Nplate™ therapy: _____ (x 10^9/L) At Time of Event: _____ (x 10^9/L) After Event: _____ (x 10^9/L)

3. Safety Information

Event:

Serious Event[2]: ☐ Yes ☐ No | Date of Event: ___ /___ / _____ (MM/DD/YY)

If serious, please document the reason for seriousness:

☐ Death ☐ Life-threatening

☐ Hospitalization - initial or prolonged

☐ Congenital anomaly/birth defect

☐ Persistent or significant disability/incapacity

☐ Other (*important medical events*)_____

Outcome of Event: ☐ Resolved ☐ Resolving/recovering ☐ Resolved with sequelae ☐ Not resolved

Action Taken:	
Concomitant Medications: ☐ None	
Medical History:	
Radiographic Findings: (Please send full report)	

4. Reporter Information

	Prescriber Name/Title (Print)	NEXUS Program ID # (found on enrollment confirmation fax)	Date of report: ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			
☐ Institution			Signature

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

1N/A : Not Applicable2 An adverse event is SERIOUS (SAE) when the patient outcome is: 1) Death – 2) Life threatening – 3) Hospitalization – initial or prolonged – 4) Significant disability/incapacity 5) Congenital anomaly/birth defect - 6) Other (important medical events)

Nplate™ (romiplostim) NEXUS Program: Hematological Malignancy/MDS

1. Patient Information / Nplate™ Administration Information

Initials: _____	NEXUS Program ID: _____	☐ Male ☐ Female	Date of Birth: ___ /___ / _____ (MM/DD/YY)

Nplate™ Start Date: ___ /___ / _____ (MM/DD/YY)	Is Nplate™ still being administered? ☐ Yes ☐ No	If YES, what is the current dose? ___ µg/kg If NO, enter date and dose of last administration ___ /___ / _____ (MM/DD/YY) _____ µg/kg

2. Safety Information

Event: New : ☐ Yes ☐ No

Serious Event[1]: ☐ Yes ☐ No

If serious, please document the reason for seriousness:

☐ Death ☐ Life-threatening

☐ Hospitalization - initial or prolonged ☐ Congenital anomaly/birth defect

☐ Persistent or significant disability/incapacity ☐ Other (*important medical events*)_____

Outcome of Event: ☐ Resolved ☐ Resolving/recovering ☐ Resolved with sequelae ☐ Not resolved

Date of Diagnosis: ___ /___ / _____ (MM/DD/YY)

Please indicate appropriate diagnosis or ☐ Under Investigation

Peripheral Blood Smear Abnormal ☐ Yes ☐ No

☐ AML (FAB subtype): _____	☐ Myeloproliferative Disease (MPD) (Specify): ☐ CML ☐ PV ☐ IMF ☐ ET	☐ Lymphoma (specify): _____
☐ MDS (IPSS score): _____		☐ Other (specify): _____

What clinical features were present at the time of diagnosis? (check all that apply)

☐ anemia ☐ thrombocytopenia ☐ granulocytopenia ☐ pallor ☐ fatigue
☐ increased bruising/bleeding ☐ lymphadenopathy ☐ fever/night sweats
☐ recurrent infection/poor wound healing ☐ abdominal pain and/or loss of appetite
☐ bone pain ☐ hepatosplenomegaly ☐ loss of efficacy to Amgen product
☐ Other (specify): _____

1 An adverse event is SERIOUS (SAE) when the patient outcome is: 1) Death – 2) Life threatening – 3) Hospitalization – initial or prolonged – 4) Significant disability/incapacity 5) Congenital anomaly/birth defect - 6) Oher (important medical events)

Nplate™ (romiplostim) NEXUS Program: Hematological Malignancy/MDS

3. Medical History

Bone Marrow Studies:

Bone marrow aspirate	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Silver stain:	☐ Positive	☐ Negative	☐Not done
Bone marrow biopsy	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Trichrome stain:	☐ Positive	☐ Negative	☐Not done
Immunophenotype	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____		
Cytogenetics	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____		

Concomitant Medications:

☐ Corticosteroids ☐ IVIg ☐ Danazol ☐ Rituximab ☐ Interferon alpha ☐ Azathioprine:
☐ Cyclophosphamide ☐ Other (specify): _____ ☐ None

If the malignant diagnosis documented in section 2 (previous page) is progression or transformation of a pre-existing disease, when was the disease first diagnosed? ___/___/___ (MM/DD/YY)

4. Reporter Information

	Prescriber Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ___/___/_____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ **Signature**
☐ Institution			

Please fax the completed form to The Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

Nplate™ (romiplostim) NEXUS Program: Medication Errors Associated with Serious Outcomes

1. Patient Information			
Initials: _____	NEXUS Program ID: _____	☐ Male ☐ Female	Date of Birth: ___ /___ / _____ (MM/DD/YY)

2. Nplate™ Administration Information	
Nplate™ Start Date: ___ /___ / _____ (MM/DD/YY)	Latest/last Dose Received: _____ µg/kg Intended dose: _____ µg/kg
Nplate™ Stop Date: ___ /___ / _____ (MM/DD/YY) or ☐ N/A	Platelet Count at Time of Event: _____ (x 10^9/L)

3. Safety Information	
Event:	Date of Event: ___ /___ / _____ (MM/DD/YY)
Outcome of Event: ☐ Resolved ☐ Resolving/recovering ☐ Resolved with sequelae ☐ Not resolved	
Action Taken:	
Concomitant Medications: ☐ None	
Medical History:	
Description of Event:	

4. Reporter Information			
	Prescriber Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ **Signature**
☐ Institution			

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

Nplate™ (romiplostim) NEXUS Program: Bone Marrow Reticulin / Bone Marrow Fibrosis

1. Patient Information

Initials: _____	NEXUS Program ID: _____	☐ Male ☐ Female	Date of Birth: ___ /___ / _____ (MM/DD/YY)

2. Nplate™ Administration Information

Nplate™ Start Date: ___ /___ / _____ (MM/DD/YY)	Is Nplate™ still being administered? ☐ Yes ☐ No	If YES, what is the current dose? ___ µg/kg If NO, enter date and dose of last administration ___ /___ / _____ (MM/DD/YY) _____ µg/kg

3. Safety Information

Event: ☐ Bone marrow reticulin ☐ Bone marrow fibrosis

Serious Event[1]: ☐ Yes ☐ No | Date of Event: : ___ /___ / _____ (MM/DD/YY)

If serious, please document the reason for seriousness:
☐ Death ☐ Life-threatening
☐ Hospitalization - initial or prolonged ☐ Congenital anomaly/birth defect
☐ Persistent or significant disability/incapacity ☐ Other (*important medical events*)_____

Outcome of Event: ☐ Resolved ☐ Resolving/recovering ☐ Resolved with sequelae ☐ Not resolved

Peripheral Blood Smear Abnormal ☐ Yes ☐ No

Bone Marrow Studies (Please note below, and attach reports)

Bone marrow aspirate	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Silver stain: ☐ Positive ☐ Negative ☐ Not done	
Bone marrow biopsy	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Trichrome stain: ☐ Positive ☐ Negative ☐ Not done	
Immunophenotype	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____
Cytogenetics	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____

What clinical features were present at the time of diagnosis? (check all that apply)

☐ Anemia ☐Thrombocytopenia ☐Granulocytopenia
☐ Hepatomegaly ☐Splenomegaly
☐ Increased nucleated red blood cells (nRBCs) ☐Increased peripheral blast cells
☐ Increased bruising/bleeding ☐Loss of efficacy to Nplate™
☐ Other (specify): _____

Please quantify the degree of bone marrow reticulin/collagen using the Bauermeister scale (check only one):

0 ☐	No reticulin fibers demonstrable
1 ☐	Occasional fine individual fibers and foci of a fine fiber network
2 ☐	Fine fiber network throughout most of the section; no coarse fibers
3 ☐	Diffuse fiber network with scattered thick coarse fibers but no mature collage (negative trichrome stain)
4 ☐	Diffuse, often coarse fiber network with areas of collagenization (positive trichrome stain)
☐ Other (please describe): _____	

1 An adverse event is SERIOUS (SAE) when the patient outcome is: 1) Death – 2) Life threatening – 3) Hospitalization – initial or prolonged – 4) Significant disability/incapacity 5) Congenital anomaly/birth defect - 6) Oher (important medical events)

Nplate™ (romiplostim) NEXUS Program: Bone Marrow Reticulin / Bone Marrow Fibrosis

3. Medical History

Were any of the following procedures performed **prior to** the onset of treatment with Nplate™?
(e.g., is there baseline documentation of any of the following assessments?)

Bone marrow aspirate	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Silver stain: ☐ Positive ☐ Negative ☐Not done	
Bone marrow biopsy	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Trichrome stain: ☐ Positive ☐ Negative ☐Not done	
Immunophenotype	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____
Cytogenetics	☐ Yes ☐ No	___/___/___ (MM/DD/YY)	Abnormalities: ☐ Yes ☐ No	If YES, specify: _____

Concomitant Medications:

☐ Corticosteroids ☐ IVIg ☐ Danazol ☐ Rituximab ☐ Interferon alpha ☐ Azathioprine
☐ Cyclophosphamide ☐ Other (specify): _____ ☐ None

4. Reporter Information

	Prescriber Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ____/____/_____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ **Signature**
☐ Institution			

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

Nplate™ (romiplostim) NEXUS Program: Worsened Thrombocytopenia after Cessation of Treatment with Nplate™

1. Patient Information

Initials: _____	NEXUS Program ID: _____	☐ Male ☐ Female	Date of Birth: ___ /___ / _____ (MM/DD/YY)

2. Nplate™ Administration Information

Nplate™ Start Date: ___ /___ / _____ (MM/DD/YY)	Platelet Count prior to initiation of Nplate™ therapy :_____ (x 10^9/L)
Nplate™ Stop Date: ___ /___ / _____ (MM/DD/YY)	Platelet Count at Time of Event: _____ (x 10^9/L)
	Latest/last Dose Received: _____ µg/kg

3. Safety Information

Serious Event[1]: ☐ Yes ☐ No	Date of Event: ___ /___ / _____ (MM/DD/YY)

If serious, please document the reason for seriousness:

☐ Death ☐ Life-threatening

☐ Hospitalization - initial or prolonged ☐ Congenital anomaly/birth defect

☐ Persistent or significant disability/incapacity ☐ Other (*important medical events*)_____

Outcome of Event: ☐ Resolved ☐ Resolving/recovering ☐ Resolved with sequelae ☐ Not resolved

Action Taken:	
Concomitant Medications: ☐ None	
Medical History:	
Description of Event:	

4. Reporter Information

	Prescriber Name/Title (Print)	**NEXUS Program ID # (found on enrollment confirmation fax)**	**Date of report:** ___ /___ / _____ (MM/DD/YY)
☐ NEXUS Specialist			
☐ Healthcare Provider			_____ **Signature**
☐ Institution			

Please fax the completed form to the Nplate™ NEXUS Program 1-877-675-2830
If you have questions, please contact the Nplate™ NEXUS Program at 1-877-675-2831

1 An adverse event is SERIOUS (SAE) when the patient outcome is: 1) Death – 2) Life threatening – 3) Hospitalization – initial or prolonged – 4) Significant disability/incapacity 5) Congenital anomaly/birth defect - 6) Other (important medical events)

Nplate™ (romiplostim)
REMS
MONITORING AND COMPLIANCE OF Nplate™ NEXUS PROGRAM ELEMENTS

Metrics

Every month, the Nplate™ NEXUS Program will generate the following metrics:

- Number of new and ongoing patients and HCPs enrolled into the Nplate™ NEXUS Program
- Number of patients enrolled in each ICD-9 code and diagnosis provided upon patient enrollment
- The expected number of completed Nplate™ NEXUS Program Safety Questionnaires and the actual number of questionnaires completed.
- The number of patients discontinued from the program and the percentage who have a completed Nplate™ NEXUS Program Patient Discontinuation/Post-Discontinuation Follow-Up Form on file
- Cumulative and monthly number of adverse events based on risks associated with Nplate™ therapy

These metrics will be reviewed and reconciled to assure that Nplate™ is distributed only in accordance with the Nplate™ NEXUS Program.

Monitoring Enrollment of Nplate™ Prescribers and Patients

As part of enrollment process, the HCP attests to enrolling all Nplate™ patients into the Nplate™ NEXUS Program prior to therapy. In order to monitor enrollment and verify that all patients are enrolled in the Nplate™ NEXUS Program the following audits will be conducted:

- **Order monitoring:** The Nplate™ NEXUS Program verifies that the ordering HCP is enrolled in the program and is treating active patients prior to shipping Nplate™.

- **Vials shipped monitoring**: An audit system will be in place to compare Nplate™ shipments to active patients enrolled in the program. For each HCP or Institution, shipment volumes will be compared to expected volumes based on historical purchase patterns and volume expectations based on the number of enrolled patients. Shipment volumes that are outside of expected parameters will be investigated and resolved by contacting the HCP or Institution and reconciling the shipment to patients treated.

  The initial proposed audit criteria is that every four weeks, the number of vials shipped to an HCP or institution is compared to the number of enrolled patients. If more than 2 vials per enrolled patient week are shipped, the HCP or Institution is flagged for follow up. If an HCP or Institution is flagged for any 8 week period, then the Nplate™ NEXUS Program will contact the HCP or Institution and reconcile the last 4 weeks of shipments. Audit criteria will be assessed on an ongoing basis and amended as appropriate.

In addition, in the analysis of the number of vials shipped per enrolled patient week, purchase pattern outliers will be reviewed manually. Consistent outliers will be investigated.

- **Patient roster monitoring:** As part of the 6-month safety monitoring, the Nplate™ NEXUS Program will confirm the roster of actively treated patients. HCP will be presented with the roster of active patients according to Nplate™ NEXUS Program records and requested to confirm their status.

Hospital/Institution Program Compliance

Amgen will implement a review process to detect potential institution noncompliance with the program and/or suspected drug diversion.

On a semiannual basis, Amgen will perform a review of a select sample of institutions to assess their degree of compliance with the program. The sample size will be of at least 5% of the total number of enrolled institutions and consist of randomly selected institutions and/or institutions for which the number of vials shipped over a set period of time does not appear to be consistent with the expected usage based on the number of patients treated at the institution (e.g., more than 8 vials per enrolled hospitalized patients over 4 weeks).

The reviewed institutions will be contacted and asked to provide copies of their drug reconciliation and accountability records for the set time period. The information requested from the drug reconciliation and accountability records will include:

- Date of prescription
- Name of enrolled prescribing HCP
- Patient name and birthday
- Number of vials dispensed to the patient
- Overall inventory for set period of time including: total number of vials ordered, dispensed, and in inventory

Based on the records provided, Amgen will confirm that all prescribing HCP and patients receiving Nplate™ are enrolled in the program. If the discrepancy can be resolved through the provided records, the institution will be "un-flagged" and no further actions will be required. If the discrepancy cannot be resolved through the provided records, Amgen will schedule a personal assistance on-site visit to assist the institution with the process and the program requirements. Institutions that are repeatedly noncompliant with the program will be subject to

corrective measures, additional reviews, and ultimately required to match each drug order with specific patients.

Healthcare Provider or Institution Noncompliance and Dis-enrollment

If during the program Amgen finds that a HCP or institution is not compliant with the program, all reasonable efforts will be taken to contact the HCP and discuss Amgen's relevant concerns.

- Should the noncompliant HCP or Institution continue to be noncompliant with the program requirements, such a HCP will not be allowed to enroll new patients into the Nplate™ NEXUS Program. Any HCP or Institution can be dis-enrolled from the Nplate™ NEXUS Program if they do not adhere to the requirements set forth in the Nplate™ NEXUS Program HealthCare Provider Enrollment Form or the Nplate™ NEXUS Program Institution Enrollment Form and this will be communicated by the Nplate™ NEXUS Program. However, in recognition of potential medical consequences resulting from sudden drug discontinuation for those patients currently enrolled in the program and who continue to meet enrollment criteria Amgen will continue to fulfill orders for Nplate™ (romiplostim). The dis-enrolled HCP or Institution will continue to be able to order Nplate™ for existing enrolled patients; however, will not be able to enroll new patients into the Nplate™ NEXUS Program. Nevertheless, Amgen will continue on a case-by-case basis to engage with the HCP and encourage resolution of the outstanding concerns.
- The number of HCPs who were noted to be non-compliant and have dis-enrollment procedures initiated will be monitored.

Assessing and Minimizing Unintended Consequences of the REMS

It will be important to minimize unintended consequences and burden on the healthcare system by continuous reevaluation of the Nplate™ benefit-risk profile as the program is implemented. Based on the findings of the updated benefit-risk assessment, the REMS should be redesigned with the minimum interventions necessary to adequately minimize the documented risks.

Amgen will conduct market research with HCPs and patients to assess the following to inform further revisions to the Program:

- HCP awareness, knowledge, and attitude toward the benefit-risk information for Nplate™.
- Patient comprehension of the benefit-risk information discussed in the Nplate™ Medication Guide.
- HCP and patient evaluation of the program convenience and ease of use.

Through these analyses, Amgen will also gather feedback from HCPs on the utility in clinical practice of the tools and materials contained in the Nplate™ NEXUS Program Training Kit, and the Nplate™ NEXUS Program. The feedback received will be utilized in assessing and improving the efficacy of this REMS.