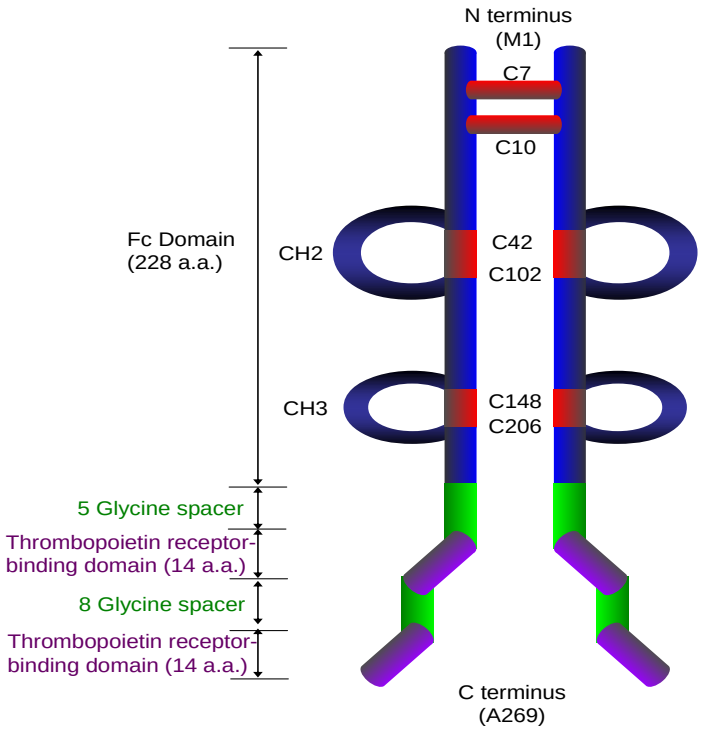
NAME OF THE MEDICINE

Nplate® is the Amgen Inc. trademark for romiplostim (rbe).



CAS number: 267639-76-9

DESCRIPTION

Romiplostim, a member of the thrombopoietin (TPO) mimetic class, is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as c-Mpl) to increase platelet production. The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor-binding domains. Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*).

Nplate is a sterile, white, preservative-free, lyophilised powder for reconstitution and administration as a subcutaneous (SC) injection.

Nplate contains the active ingredient, romiplostim and the following inactive ingredients: mannitol, sucrose, histidine, polysorbate 20 and hydrochloric acid – dilute (for pH adjustment).

PHARMACOLOGY

Pharmacodynamics

Romiplostim increases platelet production through binding and activation of the thrombopoietin receptor, a mechanism analogous to endogenous thrombopoietin (eTPO). The TPO receptor is predominately expressed on cells of the myeloid lineage such as megakaryocyte progenitor cells, megakaryocytes and platelets.

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet count. The peak platelet counts in immune (idiopathic) thrombocytopenic purpura (ITP) patients who received a single subcutaneous dose of 1 - 10 µg/kg Nplate were 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 week period; the response was variable among patients. The platelet counts of ITP patients who received doses of 1 or 3 µg/kg Nplate at weekly intervals for 6 weeks were within the range of 50 to 450 x 10^9/L for most patients, but the response was variable. Individual dose adjustment of Nplate is recommended, and the dose adjustment should be based on the observed platelet count (see **DOSAGE AND ADMINISTRATION**).

Pharmacokinetics

The pharmacokinetics of romiplostim involves target-mediated disposition through binding to the TPO receptors on the platelets and megakaryocytes. This results in non-linear volume of distribution and clearance.

The serum concentration of romiplostim administered at pharmacologically active doses (< 3 µg/kg) was not measurable in most samples collected from healthy volunteers and patients with ITP, despite the use of a very specific and sensitive ELISA with a lower limit of quantification of 18 pg/mL.

In patients with ITP who received chronic weekly treatment of Nplate subcutaneously (median duration of treatment 39 weeks, with up to 84 weeks for 100 patients), the pharmacokinetics of romiplostim over the dose range of 3 to 15 µg/kg indicated that peak serum concentrations were observed about 7 to 50 hours post-dose (median: 14 hours). The half-life values ranged 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 of romiplostim and vice versa. In another ITP clinical study no accumulation in serum concentrations was observed after weekly administration of 3 µg/kg Nplate for 6 weeks.

Special populations

Elderly

The pharmacokinetic profile has not been assessed in the elderly.

Paediatric

The pharmacokinetic profile has not been assessed in those ≤18 years.

Impaired hepatic function

The pharmacokinetic profile has not been assessed in patients with impaired hepatic function.

Impaired renal function

The pharmacokinetic profile has not been assessed in patients with impaired renal function.

CLINICAL TRIALS

The safety and efficacy of Nplate was evaluated in two Phase 3, randomised, placebo-controlled, double-blind studies in adults with chronic ITP. Patients had completed at least one treatment and had a platelet count of $\leq 30 \times 10^9$/L prior to study entry; they are representative of the entire spectrum of such ITP patients.

Study 1 evaluated patients who had not undergone a splenectomy and had an inadequate response or were intolerant to prior ITP therapies. Patients had been diagnosed with ITP for approximately 2 years at the time of study entry. Patients had a median of 3 (range 1 to 7) treatments for ITP prior to study entry and a median platelet count of 19×10^9/L. Study 2 evaluated patients who had undergone a splenectomy and continued to have thrombocytopenia. Patients had been diagnosed with ITP for approximately 8 years at the time of study entry. In addition to a splenectomy, patients had a median of 6 (range 3 to 10) treatments for ITP prior to study entry. Their median platelet count was 14×10^9/L at study entry.

With exception of splenectomy status, study design was the same for both studies. Patients (≥ 18 years) were randomised in a 2:1 ratio to receive a starting dose of Nplate 1 µg/kg or placebo. Patients received single weekly SC injections for 24 weeks. Doses were adjusted to maintain platelet counts (50 to 200×10^9/L). In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response. A durable platelet response was defined as a weekly platelet count $\geq 50 \times 10^9$/L for at least 6 weeks during weeks 18 through 25 in the absence of rescue therapy at any time during the treatment period. In the placebo-controlled studies, the most frequently used weekly dose for splenectomised patients was between 2 and 7 µg/kg (25^{th}-75^{th} percentile respectively; median 3 µg/kg). For non-splenectomised patients, it was between 1 and 3 µg/kg (25^{th}-75^{th} percentile respectively; median 2 µg/kg).

A significantly higher proportion of patients receiving Nplate achieved a durable platelet response compared to patients receiving placebo in both studies: Study 1, 61% versus 5% and Study 2, 38% versus 0%, respectively (see Table 1). Treatment with Nplate provided significant improvements compared to placebo in both clinical studies for all efficacy endpoints for all patients randomised to the studies based on an intention to treat analysis (see Table 1).

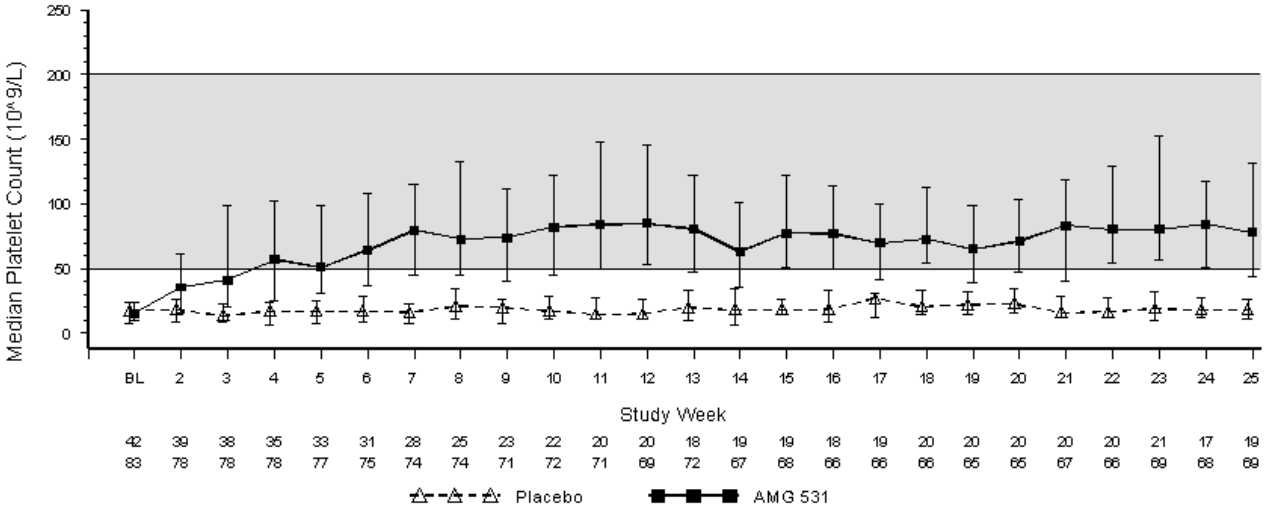
Table 1. Summary of Efficacy Results from Placebo-controlled Studies

	Study 1 Non-splenectomised Patients		Study 2 Splenectomised Patients		Combined Studies 1 & 2	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)	Nplate (n = 83)	Placebo (n = 42)
Primary Endpoint						
No. (%) Patients with Durable Platelet Response[a]	25 (61%)	1 (5%)	16 (38%)	0 (0%)	41 (50%)	1 (2%)
(95% CI)	(45%, 76%)	(0%, 24%)	(24%, 54%)	(0%, 16%)	(38%, 61%)	(0%, 13%)
p-value	<0.0001		0.0013		<0.0001	
Key Secondary Endpoints						
No. (%) Patients with Overall Platelet Response[b]	36 (88%)	3 (14%)	33 (79%)	0 (0%)	69 (83%)	3 (7%)
(95% CI)	(74%, 96%)	(3%, 36%)	(63%, 90%)	(0%, 16%)	(73%, 91%)	(2%, 20%)
p-value	<0.0001		<0.0001		<0.0001	
Mean No. Weeks with Platelet Response[c]	15	1	12	0	14	1
(SD)	7.5	3.5	7.9	0.5	7.8	2.5
p-value	<0.0001		<0.0001		<0.0001	
No. (%) Patients Requiring Rescue Therapies[d]	7 (17%)	13 (62%)	11 (26%)	12 (57%)	18 (22%)	25 (60%)
(95% CI)	(7%, 32%)	(38%, 82%)	(14%, 42%)	(34%, 78%)	(13%, 32%)	(43%, 74%)
p-value	0.0004		0.0175		<0.0001	
No. (%) Patients with Durable Platelet Response with Stable Dose[e]	21 (51%)	0 (0%)	13 (31%)	0 (0%)	34 (41%)	0 (0%)
(95% CI)	(35%, 67%)	(0%, 16%)	(18%, 47%)	(0%, 16%)	(30%, 52%)	(0%, 8%)
p-value	0.0001		0.0046		<0.0001	

[a] Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for study weeks 18-25 in the absence of rescue therapy any time during the treatment period.
[b] Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during study weeks 2-25, but without durable platelet response. Patient may not have a weekly response within 8 weeks after receiving rescue therapy.
[c] Number of weeks with platelet response is defined as number of weeks with platelet counts ≥ 50 x 10^9/L during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving rescue therapy.
[d] Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue therapy were not considered for durable platelet response. Rescue therapies allowed in the study were normal human immunoglobulin (IVIG), platelet transfusions, anti-RhD immunoglobulin, and corticosteroids.
[e] Stable dose was defined as dose maintained within ± 1 µg/kg during the last 8 weeks of treatment.

In both Phase 3 studies, 30% of patients treated with Nplate achieved a platelet count above 50 x 10^9/L by week 2, 54% by week 4, and 50% to 70% of patients maintained platelet counts ≥ 50 x 10^9/L for the remainder of the treatment period. In the placebo group, 0% to 7% of patients were able to achieve a platelet count response during the 6 months of treatment. Figure 1 shows the median weekly platelet counts over the 6 months of treatment in the treatment period.

Figure 1. Median Weekly Platelet Counts in Phase 3 Studies[a]



[a] Full analysis set includes all randomised patients excluding platelet counts within 8 weeks after rescue therapy
Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and predose day 1.

Following discontinuation of Nplate during both studies, seven patients maintained platelet counts of ≥ 50 x 10^9/L until week 36 without requiring further treatment with Nplate, and were therefore not enrolled in the long-term open-label extension study.

Reduction in Permitted Concurrent ITP Medical Therapies

In both placebo-controlled, double-blind studies, patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the study (i.e. corticosteroids, danazol and/or azathioprine). Twenty-one non-splenectomised and 18 splenectomised patients received on-study ITP medical treatments (primarily corticosteroids) at the start of study. All splenectomised patients who were receiving Nplate were able to reduce the dose by more than 25% or discontinue the concurrent ITP medical therapies by the end of the treatment period compared to 17% of the placebo-treated patients. Seventy three percent of non-splenectomised patients receiving Nplate were able to reduce the dose by more than 25% or discontinue concurrent ITP medical therapies by the end of the study compared to 50% of placebo-treated patients.

Use of Rescue Therapies

Rescue therapies (i.e. corticosteroids, normal immunoglobulin (IVIG), platelet transfusions, anti-D Rho immunoglobulin) were permitted in both placebo-controlled, double-blind studies for bleeding, wet purpura, or if the patient was at immediate risk of bleeding. The total incidence of rescue therapy use was considerably higher for placebo-treated patients than for Nplate treated patients (see Table 1).

Use of Nplate in Non-Splenectomised ITP Patients Compared with Medical Standard of Care (SOC)

Study 3 was an open-label study evaluating the safety and efficacy of Nplate compared with medical standard of care (SOC) treatment in non-splenectomised adult patients (aged ≥ 18 years) with ITP and platelet counts < 50 x 10^9/L, who received at least one prior standard therapy for ITP. Patients had a median platelet count at enrolment of 29 x 10^9/L. Medical SOC treatments were selected and prescribed by the investigator according to standard institution practices or therapeutic guidelines.

Patients were randomised in a 2:1 ratio to receive a starting dose of Nplate 3 µg/kg or SOC. Nplate was administered by single weekly SC injections for 52 weeks. Doses were adjusted throughout the study within a range of 1 to 10 µg/kg in order to maintain platelet counts (50 to 200 x 10^9/L). Of the 157 patients randomised to receive Nplate, the median (range) duration of exposure was 52.0 weeks (2 to 53). The most frequently used weekly dose was between 3 and 5 µg/kg (25^{th} - 75^{th} percentile respectively; median 3 µg/kg).

For both co-primary endpoints, the Nplate group showed significantly greater improvement (i.e., lower rate of splenectomy and lower rates of treatment failure) compared to patients assigned to receive SOC. As shown in Table 2, the odds of undergoing a splenectomy is significantly lower in the Nplate group than the SOC group, with an odds ratio (Nplate vs. SOC) of 0.17 (95% CI: 0.15, 0.61).

Table 2. Summary of Efficacy Results from Open-label Study

	Study 3 Non-splenectomised Patents	
	Nplate (n = 157)	Standard of Care (SOC) (n = 77)
Incidence rate of Splenectomy[a]	14 (8.9%)	28 (36.4%)
(95% CI)	(5%, 14.5%)	(25.7%, 48.1%)
p-value[b]	<0.0001	
Incidence of treatment failure[c]	18 (11.5%)	23 (29.9%)
(95% CI)	(6.9%, 17.5%)	(20%, 41.4%)
p-value[b]	0.0005	

[a] Patients with discontinued study during treatment period prior to reporting a splenectomy were considered as having a splenectomy.

[b] From stratified Cochran-Mantel-Haenszel (CMH) controlling for the geographic region of investigational sites (North America, European Union, and Australia).

[c] Patients who discontinued study during treatment period prior to observing a treatment failure were considered as having had a treatment failure. Treatment failure: platelet count ≤ 20 x 10^9/L for 4 consecutive weeks at the highest recommended dose and schedule, or major bleeding event, or change in therapy due to intolerable side-effects or bleeding symptoms.

Long-term Extension Study

Patients who had completed a prior Nplate study (including the Phase 3 studies) were allowed to enrol in a long-term open-label extension study. Subjects were enrolled after completing a previous romiplostim ITP study. Following subsequent amendments there was no requirement for subjects to wait until platelet counts had fallen to < 50 x 10^9/L, and to wash out certain ITP treatments prior to entering the study.

Patients in the long-term extension continued with weekly dosing and individual dose adjustments of Nplate based on platelet counts. Patients who had received placebo in

the placebo-controlled studies received an initial dose of 1 µg/kg Nplate in the extension study. Patients who were treated with Nplate in the placebo-controlled studies were re-initiated at their previous dose of Nplate, if the Nplate-free period was <24 weeks; if >24 weeks, patients received an initial dose of 1 µg/kg Nplate. The majority of patients treated with Nplate responded quickly, reaching a median count of 50 x 10^9/L after receiving 1 to 3 doses of Nplate. These platelet counts were maintained within the therapeutic range of 50 to 200 x 10^9/L throughout the remainder of the study.

Results from an integrated analysis of patients from the placebo-controlled studies who continued into the extension study support the long-term use of Nplate (median duration 78 weeks, with 292 adult patients treated for up to 277 weeks).

After the initial dose adjustment period, the majority (> 75%) of adult patients were able to maintain their dose within 2 µg/kg, suggesting maintenance of clinical effect over time in the absence of significant Nplate dosage increases. The overall incidence of rescue medication use in adult patients was 33.3%. Approximately 13% (37/292) of adult patients entered this study on concurrent ITP therapy. Twenty (54.1%) of these patients discontinued concurrent ITP therapy by the end of the study. Patients who had bone marrow biopsies (n = 38) showed no evidence of type I collagen. However, trichrome staining for type I collagen was inconsistently performed.

Data from patients previously treated with Nplate in one of the placebo-controlled studies confirm the ability of Nplate to sustain a response over an extended period of time in the majority of patients. In addition, these data demonstrate the ability of Nplate to increase platelet counts in patients from the studies who previously received placebo. Former placebo patients who received Nplate in the extension study showed a pattern of platelet count increases similar to patients who received Nplate in the pivotal studies.

Due to the heterogeneity of the population with regard to inclusion criteria, disease baseline characteristics, treatment history, concurrent medication, Nplate dose received and length of treatment included in this study, data on the long-term efficacy and safety of Nplate should be interpreted with caution.

INDICATIONS

Nplate is indicated for treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):

- who are non-splenectomised and have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins;
- who are splenectomised and have had an inadequate response to splenectomy.

CONTRAINDICATIONS

Nplate is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, romiplostim, or any other component of the product (see **DESCRIPTION**).

PRECAUTIONS

General

Nplate should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk of bleeding. Nplate should not be used in an attempt to normalise the platelet count.*

The following special warnings and precautions are observed or theoretical class effects of TPO receptor stimulators.

Recurrence of Thrombocytopenia After Cessation of Treatment

Thrombocytopenia is likely to recur upon discontinuation of Nplate; some patients may develop thrombocytopenia of greater severity than was present prior to Nplate*. There is increased risk for bleeding if Nplate is discontinued in the presence of anticoagulants or anti-platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of Nplate. It is recommended that, if treatment with Nplate is discontinued, weekly complete blood counts be obtained for at least 2 weeks and alternative ITP treatment for worsening thrombocytopenia be considered according to current treatment guidelines.* Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support.

Serious life-threatening or fatal bleeding events after discontinuation of Nplate have been reported.*

Increased Bone Marrow Reticulin

Reticulin has been observed in the bone marrow of some ITP patients prior to treatment with Nplate and appeared to increase in some patients treated with Nplate. Increased bone marrow reticulin is believed to be due to the increased number of megakaryocytes in the bone marrow which may subsequently release cytokines. In clinical studies with Nplate, reticulin has not been associated with adverse clinical sequelae, cases of chronic idiopathic myelofibrosis (CIMF), or secondary myelofibrosis, and may improve upon discontinuation of Nplate. Increased reticulin can be detected through bone marrow biopsy and may be suggested by morphological changes in the peripheral blood cells.

Prior to and during treatment with Nplate, examine peripheral blood smears and complete blood counts for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If a patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Nplate and consider performing a bone marrow biopsy, with appropriate staining for fibrosis. Cytogenetic analysis of the bone marrow sample for clonal abnormality should also be considered.

The long term risk for progression to myelofibrosis is unknown.*

Thrombotic/Thromboembolic Complications

Platelet counts above the normal range present a theoretical risk for thrombotic/ thromboembolic complications. The incidence of thrombotic/thromboembolic events observed in the control groups were comparable to Nplate in clinical studies. No

association between these events and elevated platelet counts was observed. Dose adjustment guidelines should be followed (see **DOSAGE AND ADMINISTRATION**).

In the postmarketing setting, thrombotic/thromboembolic events have been observed (see **ADVERSE EFFECTS: Postmarketing Experience**).

To minimise the risk for thrombocytosis, do not use Nplate in an attempt to "normalise" platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of ≥ 50 x 10^9/L (see DOSAGE AND ADMINISTRATION).*

Cases of thromboembolic events including portal vein thrombosis have been reported in patients with chronic liver disease receiving Nplate. Nplate should be used with caution in these populations.*

Caution should be used when administering Nplate to patients with known risk factors for thromboembolism including but not limited to inherited (eg Factor V Leiden) or acquired risk factors (eg ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking.*

Risk of Progression of Myeloid Malignancies or Existing Myelodysplastic Syndromes (MDS)

TPO receptor stimulators are haematopoietic growth factors that lead to thrombopoietic progenitor cell expansion, differentiation, and platelet production. The TPO receptor is predominantly expressed on the surface of cells of the myeloid lineage; there is no confirmed expression of the TPO receptor on solid tumours. TPO has been shown to stimulate the proliferation of a subset of acute myeloblastic leukaemia cells *in vitro*. There is therefore a theoretical concern that romiplostim may stimulate the progression of existing myeloid malignancies or MDS.

In clinical studies of treatment with Nplate in patients with MDS, cases of progression to acute myeloid leukaemia (AML), a potential clinical outcome of MDS, were reported. In addition, there were cases of transient blast cell increases, which did not progress to AML.* The risk-benefit profile for Nplate has not been established in MDS or other non-ITP patient populations.

A randomised, double-blind, placebo-controlled trial enrolling patients with severe thrombocytopenia and International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS was terminated due to more cases of AML observed in the Nplate treatment arm. At the time of an interim analysis, among 219 MDS patients randomized 2:1 to treatment with Nplate or placebo (147 Nplate: 72 placebo), 11 patients showed progression to AML, including nine on the Nplate arm versus two on the placebo arm. In addition, in peripheral blood counts, the percentage of circulating myeloblasts increased to greater than 10% in 28 patients, 25 of whom were in the romiplostim treatment arm. Of the 28 patients who had an increase in circulating myeloblasts to greater than 10%, eight of these patients were diagnosed to have AML and 20 patients had not progressed to AML. In four patients, increased peripheral blood blast cell counts decreased to baseline after discontinuation of Nplate.*

Loss of Response to Nplate

A loss of response or failure to maintain a platelet response with Nplate should prompt a search for causative factors including neutralising antibodies to Nplate (see

ADVERSE EFFECTS: Immunogenicity) and increased bone marrow reticulin (see **PRECAUTIONS: Increased Bone Marrow Reticulin**).

Medication Errors*

Medication errors including overdose and underdose have been reported in patients receiving Nplate. Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue Nplate and monitor platelet counts. Reinitiate treatment with Nplate in accordance with dosing and administration recommendations. Underdose may result in lower than expected platelet counts and potential for bleeding. Platelet counts should be monitored in patients receiving Nplate (see **PRECAUTIONS: Thrombotic/Thromboembolic Complications, DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**).

Patients with Hepatic or Renal Impairment

Experience is limited in patients with severe hepatic or renal impairment. Nplate should be used with caution in these populations. Thromboembolic events have been reported in patients with chronic liver disease receiving Nplate (see Thrombotic/Thromboembolic Complications.*

Effects on Ability to Drive and Use Machines

No studies on the ability to drive and use machines have been performed with Nplate. Patients should be informed that in clinical trials mild to moderate, transient bouts of dizziness were experienced by some patients.*

Effects on Fertility

Romiplostim had no observed effect on the fertility of male and female rats at subcutaneous doses up to 100 µg/kg administered 3 times weekly (up to 9 times the serum AUC in humans at the maximum recommended clinical dose). The predictive value of this animal study is limited, however, due to the frequent development of drug-neutralising antibodies.

Use in Pregnancy

Pregnancy Category: B3

Embryofoetal development studies showed no increased in foetal abnormalities in rats given subcutaneous doses of romiplostim of up to 100 µg/kg every second day during gestation (up to 3 times the serum AUC in humans at the maximum recommended clinical dose). The predictive value of these studies is limited, though, by the low animal:human exposure level and the development of drug-neutralising antibodies in the species. In a pre- and post-natal development study in rats, stillbirths were increased and perinatal pup survival was decreased at this dose level. An increase in post-implantation loss was observed in mice receiving a subcutaneous dose of 100 µg/kg every third day.

Romiplostim crosses the placenta in rats and maternal transmission to the developing foetus may occur in humans.

There are no studies with romiplostim in pregnant women. Nplate should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Patients who use romiplostim during pregnancy or become pregnant while receiving this drug are encouraged to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Use in Lactation

It is not known whether romiplostim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nplate is administered to women who are breast-feeding.

Women who are breastfeeding while receiving this drug are encouraged to enrol in Amgen's Lactation Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Paediatric Use

The safety and efficacy of Nplate in paediatric patients (< 18 years) have not been established. In a Phase 1/2 dose finding study of 22 paediatric patients evaluated over 12 weeks, no new safety signals were identified.*

Use in the Elderly

Of 204 patients who received Nplate in ITP clinical studies, 38 (19%) were ≥ 65 years, and 18 (9%) were ≥ 75. No overall differences in safety or efficacy were observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of older individuals cannot be ruled out.*

Carcinogenicity

The carcinogenic potential of romiplostim has not been investigated. There is a theoretical concern that romiplostim may stimulate the proliferation of existing cancerous cells that express the TPO receptor (see **PRECAUTIONS: Progression of Existing Myeloid Malignancies or Myelodysplastic Syndromes**).

Genotoxicity

The genotoxic potential of romiplostim has not been investigated.

Effects on Laboratory Tests

No interactions with laboratory and diagnostic tests have been identified.

INTERACTIONS WITH OTHER MEDICINES

No formal drug-drug interaction studies of Nplate have been performed.

ITP medical therapies used in the combination with Nplate in clinical studies included corticosteroids, danazol, and/or azathiprine, normal immunoglobulin (IVIG) and anti-D Rho immunoglobulin. Platelet counts should be monitored when combining Nplate with other ITP medical therapies in order to avoid platelet counts outside of the recommended range (see **DOSAGE AND ADMINISTRATION**).

ADVERSE EFFECTS

Adverse events reported in fifteen ITP clinical trials are shown in Table 3. Based on an analysis of patients enrolled in four placebo-controlled studies, in one SOC-controlled study, and ten uncontrolled studies adverse events were reported in 1016 (94.2%) patients receiving Nplate (n=1078) and in 129 (93.5%) patients receiving placebo/SOC (n=138). The majority of these events were mild to moderate in nature, with severe, life-threatening or fatal adverse events reported in 38.4% of patients receiving placebo/SOC and in 39.6% of patients receiving Nplate.*

The most commonly reported adverse events were headache, nasopharyngitis and arthralgia.

Table 3. Adverse Events Reported in ≥ 5% incidence in ITP Patients administered Nplate or Placebo/SOC by System Organ Class and Preferred Term (ITP Safety Set 15 ITP clinical trials)*

System Organ Class Preferred Term	Nplate (n = 1078) n (%)	Placebo/SOC (n = 138) n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	103 (9.6)	9 (6.5)
Idiopathic thrombocytopenic purpura	90 (8.3)	4 (2.9)
Anaemia	66 (6.1)	6 (4.3)
Gastrointestinal disorders		
Nausea	209 (19.4)	12 (8.7)
Diarrhoea	202 (18.7)	13 (9.4)
Vomiting	113 (10.5)	7 (5.1)
Gingival bleeding	107 (9.9)	13 (9.4)
Abdominal pain	98 (9.1)	7 (5.1)
Constipation	92 (8.5)	7 (5.1)
Mouth haemorrhage	83 (7.7)	6 (4.3)
Abdominal pain upper	71 (6.6)	9 (6.5)
Toothache	38 (3.5)	7 (5.1)
General disorders and administration site conditions		
Fatigue	251 (23.3)	29 (21.0)
Oedema peripheral	135 (12.5)	5 (3.6)
Pyrexia	127 (11.8)	11 (8.0)
Pain	86 (8.0)	5 (3.6)
Asthenia	78 (7.2)	3 (2.2)
Chest pain	55 (5.1)	5 (3.6)

System Organ Class Preferred Term	Romiplostim (n = 1078) n (%)	Placebo/SOC (n = 138) n (%)
Infections and infestations		
Nasopharyngitis	282 (26.2)	26 (18.8)
Upper respiratory tract infection	196 (18.2)	13 (9.4)
Influenza	98 (9.1)	3 (2.2)
Urinary tract infection	97 (9.0)	11 (8.0)
Sinusitis	77 (7.1)	3 (2.2)
Bronchitis	74 (6.9)	4 (2.9)
Injury, poisoning and procedural complications		
Contusion	243 (22.5)	29 (21.0)
Metabolism and nutrition disorders		
Hypokalaemia	34 (3.2)	7 (5.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	253 (23.5)	16 (11.6)
Back pain	170 (15.8)	10 (7.2)
Pain in extremity	168 (15.6)	10 (7.2)
Myalgia	121 (11.2)	2 (1.4)
Musculoskeletal pain	88 (8.2)	5 (3.6)
Muscle spasms	70 (6.5)	8 (5.8)
Nervous system disorders		
Headache	390 (36.2)	33 (23.9)
Dizziness	144 (13.4)	8 (5.8)
Paraesthesia	77 (7.1)	1 (0.7)
Psychiatric disorders		
Insomnia	114 (10.6)	13 (9.4)
Anxiety	56 (5.2)	7 (5.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	244 (22.6)	34 (24.6)
Cough	187 (17.3)	13 (9.4)
Oropharyngeal pain	131 (12.2)	6 (4.3)
Dyspnoea	76 (7.1)	7 (5.1)
Nasal congestion	62 (5.8)	3 (2.2)
Rhinorrhoea	54 (5.0)	4 (2.9)
Skin and subcutaneous tissue disorders		
Petechiae	200 (18.6)	27 (19.6)
Rash	122 (11.3)	10 (7.2)
Pruritus	87 (8.1)	7 (5.1)
Ecchymosis	68 (6.3)	11 (8.0)
Vascular disorders		
Haematoma	103 (9.6)	10 (7.2)
Hypertension	63 (5.8)	6 (4.3)

Serious Adverse Events/Deaths/Withdrawals/Interventions from the two Phase 3 Placebo-controlled Studies (Study 1 and 2)

Fourteen patients (17%) treated with Nplate (n=84) experienced serious adverse events, two (2%) of whom had 3 serious adverse events assessed by the investigator as possibly related to treatment: bone marrow disorder determined to be increased reticulin, peripheral embolism, and peripheral ischemia. Eight (20%) patients treated with placebo (n=41) experienced serious adverse events.

There were four fatal adverse events during the two placebo-controlled studies (1 (1%) patient receiving Nplate and 3 (7%) placebo-treated patients); none of the deaths were considered treatment-related. The Nplate-treated patient died following an intracranial hemorrhage that occurred after Nplate was discontinued in the presence of anti-platelet therapy. The fatal adverse events in the placebo-treated patients were (n (%)): cerebral haemorrhage (1 (2%)), pulmonary embolism (1 (2%)) and primary atypical pneumonia following hospitalisation for an intracranial bleed (1 (2%)).

Twenty-five patients discontinued treatment: 5 (6.0%) patients receiving Nplate and 20 (48.8%) placebo-treated patients. Three patients treated with Nplate discontinued treatment due to serious adverse events: B-cell lymphoma in a patient with pre-existing lymphadenopathy and several lymphoid aggregates in the bone marrow, bone marrow disorder determined to be increased reticulin, and intracranial hemorrhage after discontinuation of Nplate in the presence of anti-platelet therapy. One placebo-treated patient discontinued the study because of metastases to the liver.

Eighty-three percent of patients in both Nplate and placebo groups had adverse events leading to intervention (e.g. alteration or discontinuation of study medication, other medications or therapies administered, hospitalisation). The most common adverse events leading to intervention in both the Nplate and placebo groups, respectively, were headache (29% vs. 27%), upper respiratory tract infection (13% vs. 10%), and arthralgia (12% vs. 7%).

Long-term Safety

Information on the long-term safety of Nplate is derived from the 291 adult patients in the long-term extension study. The median duration of treatment in these patients was 78 weeks (range: 1 to 277 weeks), with a median weekly dose of 4 µg/kg.

Study duration-adjusted rates were calculated in order to account for the variable amounts of time that individual patients were enrolled on study. Study duration-adjusted adverse event incidence rates were expressed as the number of events per 100 patient-years on study. Two hundred and ninety-one adult patients reported 6933 adverse events while they were receiving Nplate for a study-duration adjustment event rate of 1106.5 events per 100 patient-years on study.

The most common adverse events (study duration-adjusted event rates) were headache (65.8 events per 100 patient-years), contusion (53.8 events per 100 patient-years), epistaxis (37.0 events per 100 patient-years), nasopharyngitis (29.7 events per 100 patient-years), arthralgia (24.9 events per 100 patient-years), and fatigue (39.6 events per 100 patient-years).*

The serious adverse events expressed as study duration-adjusted event rates with >1% incidence rate were thrombocytopenia (4.9 events per 100 patient-years), ITP (2.6 events per 100 patient-years), congestive cardiac failure (2.1 events per 100 patient-years), and pneumonia (1.9 events per 100 patient-years).*

Analysis of Reported Bleeding Events

In the two Phase 3 placebo-controlled studies (Study 1 and 2) an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (≥ grade 3) bleeding events occurred at platelet counts < 30 x 10^9/L. All bleeding events > grade 2 occurred at platelet counts < 50 x 10^9/L.

The incidence of bleeding events in the two Phase 3 placebo-controlled studies (Study 1 and 2) is shown in Table 4. Nine patients reported a bleeding event that was considered serious (5 (6%) Nplate, 4 (10%) placebo). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with Nplate and 34% of patients treated with placebo (see Table 4).

Table 4. Incidence of Bleeding Events in Study 1 and 2 - Phase 3 placebo-controlled studies

Bleeding Events	Nplate (n = 84)	Placebo (n = 41)
Serious[a]	5 (6%)	4 (10%)
(Grade 2 or higher[b])	13 (15%)	14 (34%)

[a] met protocol-defined criteria for seriousness (includes any event that is fatal, life-threatening, requires hospitalisation or prolongation of hospitalisation, causes persistent or significant disability/incapacity, congenital anomaly/birth defect and any other significant hazard).
[b] Grade 1 – mild; Grade 2 – moderate; Grade 3 – severe; Grade 4 – life-threatening; Grade 5 – fatal

For the phase 3 ITP long-term safety set, the study duration-adjusted event rate of grade 2 or higher bleeding events was 98 per 100 patient-years for patients treated with Nplate and 132 per 100 patient-years for placebo-treated patients.

These trends in bleeding event rates were observed in the context of a greater reduction of concomitant ITP medications among patients receiving Nplate relative to placebo. In addition, there was a higher incidence of rescue medication use among patients receiving placebo (see **CLINICAL TRIALS: Use of Rescue Therapies**).

In study 3 (open-label study), the duration-adjusted incidence of grade 2 or higher bleeding events was 24 per 100 patient-years in patients treated with Nplate and 36 per 100 patient-years in patients receiving the standard of care.

Immunogenicity

Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Therefore, any anti-product antibodies formed are unlikely to cross react with eTPO.

Clinical trial patients were screened for immunogenicity to Nplate using an immunoassay capable of detecting both high and low affinity binding antibodies that bind to romiplostim and cross-react with eTPO. The samples that tested positive for binding antibodies were further evaluated for neutralising capacity.

In the two Phase 3 placebo-controlled studies (Study 1 and 2) the incidence of preexisting antibodies to romiplostim was 8%, and the incidence of binding antibody development during Nplate treatment was 6%. The incidence of preexisting antibodies to eTPO was 5% and the incidence of binding antibody development to eTPO during Nplate treatment was 4%. Of the patients with positive binding antibodies that

developed to romiplostim or to TPO, 0.4% of patients had neutralising activity to romiplostim and none had neutralising activity to TPO.*

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact Amgen to perform assays for antibodies.

If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralising antibodies.*

Postmarketing Experience

Cases of erythromelalgia have been reported.
Cases of hypersensitivity and angioedema have been reported.*

DOSAGE AND ADMINISTRATION

Treatment should be under the guidance of an experienced healthcare provider.

Recommended Dosage Regimen

Nplate is administered weekly as a subcutaneous injection with dose adjustments based upon the platelet count response.
Use the lowest dose of Nplate necessary to achieve and maintain a platelet count $\geq 50 \times 10^9$/L.
The prescribed Nplate dose may consist of a very small volume (e.g. 0.15 mL). Nplate should be administered only with a syringe with 0.01 mL graduations.

Initial Dose

The initial dose for Nplate is 1 µg/kg, based on actual body weight.

Dose Adjustments

Adjust the weekly dose of Nplate by increments of 1 µg/kg until the patient achieves a platelet count $\geq 50 \times 10^9$/L, but $\leq 200 \times 10^9$/L. Assess the platelet count weekly until a stable platelet count ($\geq 50 \times 10^9$/L for at least 4 weeks without dose adjustment) has been achieved. Obtain platelet counts monthly thereafter. Do not exceed a maximum weekly dose of 10 µg/kg. Adjust the dose as shown in Table 5.

Table 5. Dose Adjustment Guidance Based on Platelet Count

Platelet Count ($\times 10^9$/L)	Action
Initial dose only is 1 µg/kg based on actual body weight	
< 50	Increase dose by 1 µg/kg.
>200 for 2 consecutive weeks	Reduce the dose by 1 µg/kg.
> 400	Do not dose. Continue to assess the platelet count weekly. ▪ Reinitiate therapy when the platelet count is < 200×10^9/L at a dose reduced by 1 µg/kg.
If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of Nplate. If the patient loses response, see **PRECAUTIONS: Loss of Response to Nplate**.	

Treatment Discontinuation

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician.

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 µg/kg.

The reoccurrence of thrombocytopenia should be expected upon discontinuation of treatment (see **PRECAUTIONS: Reoccurrence of Thrombocytopenia After Cessation of Treatment**).

Use of Nplate with Concomitant Medical ITP Therapies

Medical ITP therapies used in combination with Nplate in clinical studies included corticosteroids, danazol, azathioprine, normal immunoglobulin (IVIG), and anti-D Rho immunoglobulin. If the patient's platelet count is $> 50 \times 10^9$/L, other medical ITP therapies may be reduced or discontinued (see **CLINICAL TRIALS: Reduction in Permitted Concurrent ITP Medical Therapies** and **PRECAUTIONS: Interactions with Other Medicines**).

Reconstitution

Reconstitute only with sterile Water for Injections as outlined in Table 6. Do not use saline or bacteriostatic water for injection when reconstituting the product.

Table 6. Reconstitution of Nplate single use vials

Presentation	Total amount of romiplostim per vial		Sterile Water for Injections		Extractable Product and Volume	Final Concentration
250 µg/0.5 mL	375 µg	add	0.72 mL	=	250 µg in 0.5 mL	500 µg/mL
500 µg/1 mL	625 µg	add	1.2 mL	=	500 µg in 1 mL	500 µg/mL

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

Gently swirl and invert the vial to reconstitute. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Generally, dissolution of Nplate takes less than 2 minutes. The reconstituted solution should be clear and colourless.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration; if particulates or discolouration are observed, the contents of the container should not be used.

Nplate must be used within 24 hours of reconstitution (see **PRESENTATION AND STORAGE CONDITIONS**).

Product is for single use in one patient only. Discard any residue.

No other medications should be added to solutions containing Nplate.

Dosage Calculation

To determine the injection volume to be administered, first identify the patient's total dose in micrograms using the dosing information in **DOSAGE AND**

ADMINISTRATION: Initial Dose and **Dose Adjustments**. Actual body weight at initiation of treatment should always be used when calculating the dose of Nplate. For example, a 75 kg patient initiating therapy at 1 µg/kg will commence with a dose of 75 µg. The volume of Nplate solution to be administered is calculated by dividing the microgram dose by the concentration of the reconstituted Nplate solution (500 µg/mL). For this patient example, the 75 µg dose is divided by 500 µg/mL, resulting in an injection volume of 0.15 mL.

Administration Precautions*

Caution should be used during preparation of Nplate in calculating the dose and reconstitution with the correct volume of sterile Water for Injections. Special care should be taken to ensure that the appropriate volume of Nplate is withdrawn from the vial for subcutaneous administration (see **PRECAUTIONS: Medication Errors** and **OVERDOSAGE**).

OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. If the platelet counts are excessively increased, treatment with Nplate should be discontinued and platelet counts should be monitored (see **PRECAUTIONS: Reoccurrence of Thrombocytopenia After Cessation of Treatment, Thrombotic/Thromboembolic Complications** and **Medication Errors***).
Reinitiate treatment with Nplate in accordance with **DOSAGE AND ADMINISTRATION**.

PRESENTATION AND STORAGE CONDITIONS

Nplate is available in a pack containing 1 vial of either:
- 250 µg/0.5 mL presentation: 375 µg romiplostim; extractable dose per vial is 250 µg in 0.5 mL,

or
- 500 µg/1 mL presentation: 625 µg romiplostim; extractable dose per vial is 500 µg in 1.0 mL.

Nplate should be stored at 2°C to 8°C (Refrigerate. Do not freeze). Vials should be kept in their carton to protect from light until time of use.

Reconstituted solutions of Nplate should be stored at 2°C to 8°C (Refrigerate. Do not freeze), protected from light, for up to 24 hours. However, for microbiological reasons, the reconstituted solution should be used as soon as practicable after reconstitution/preparation.

NAME AND ADDRESS OF THE SPONSOR

Amgen Australia Pty Ltd
ABN 31 051 057 428
Level 7, 123 Epping Road
North Ryde NSW 2113

Medical Information 1800 803 638

POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

8 August 2008

DATE OF MOST RECENT AMENDMENT

28 March 2014

* Please note changes in Product Information