Nplate® Physician* Education Booklet

An educational guide to Nplate® summarising safety and efficacy data; including information on the identified and potential risks associated with treatment of adult chronic ITP patients with Nplate®.

Updated 2012

*Nplate® therapy should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Please see SmPC in Appendix 1.

Table of Contents

Nplate® romiplostim [2]

Please see SmPC in Appendix 1.

1. Introduction

This guidance document has been developed for those physicians initiating and supervising Nplate® in accordance with the conditions of the Marketing Authorisation of the drug, in order to ensure its safe and effective use. It contains information to be used in conjunction with the Nplate® Summary of Product Characteristics (SmPC) and Package Leaflet (see Appendices 1 and 2).

1.1 Nplate® Overview[1,2]

Nplate® (romiplostim) is an Fc-peptide fusion protein that increases platelet production through activation of intracellular transcriptional pathways via the thrombopoietin (TPO) receptor c-Mpl, thus mimicking the action of endogenous thrombopoietin (eTPO).

1.2 Indication[1]

The approved indication for Nplate® is:

> Nplate® is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
>
> Nplate® may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.

1.3 Self-administration of Nplate.

Certain patients may be eligible for self-administration (administration outside a hospital setting) if they have been assessed weekly and have a stable platelet count (>50x10^9/l for at least 4 weeks without dose adjustment).

After the first 4 weeks of self-administration, the patient should again be supervised while reconstituting and administering Nplate, to confirm the ability to do so correctly. Only patients who demonstrate the ability to reconstitute and self-administer Nplate are allowed to continue doing so.

Platelet counts should then continue to be assessed and confirmed every 4 weeks by the healthcare provider (HCP). Training in reconstitution of the product and injection techniques must be given to any patient deemed appropriate for self-administration (see Section 2.2.6).

Please see SmPC in Appendix 1.

1.4 Patient Populations Not Studied[1]

1.4.1 Elderly patients (≥ 65 years)

No overall differences in safety or efficacy have been observed in patients < 65 and ≥ 65 years of age. Although based on these data no adjustment of the dosing regimen is required for older patients, care is advised considering the small number of elderly patients included in the clinical trials so far.

1.4.2 Children and adolescents (< 18 years)

The safety and efficacy of Romiplostim in children aged under 18 years has not yet been established. No data are available.

1.4.3 Hepatic impairment

No formal clinical studies have been conducted in this patient population. Nplate® should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) unless the expected benefit outweighs the identified risk of portal venous thrombosis in patients with thrombocytopenia associated to hepatic insufficiency treated with TPO agonists.

If the use of Nplate® is deemed necessary, platelet count should be closely monitored to minimise the risk of thromboembolic complications.

1.4.4 Renal impairment

No formal clinical studies have been conducted in this patient population. Nplate® should be used with caution in this population.

PHYSICIANS SHOULD DISCUSS THE SAFETY AND EFFICACY OF NPLATE® THERAPY WITH PATIENTS SO THAT THEY CLEARLY UNDERSTAND THE RISKS AND BENEFITS ASSOCIATED WITH THIS TREATMENT.

Physicians are also reminded that Adverse Events and Medication Errors with Nplate should be reported. Reporting forms and information can be downloaded from the Medicines Authority's website at http://medicinesauthority.gov.mt/.

Adverse events can also be reported to Amgen Europe BV or local representatives Cherubino Ltd

Please see SmPC in Appendix 1.

2. Safety

2.1 Summary of Safety

Increased bone marrow reticulin; progression of existing Myelodysplastic Syndromes (MDS); thrombocytosis and reoccurrence of thrombocytopenia after cessation of Nplate®; thrombotic/thromboembolic complications; and medication errors are all identified risks associated with Nplate® treatment.

Potential risks with Nplate® treatment include neutralising antibodies that cross react with eTPO and off-label use

The most common adverse reactions are presented in a table within the "Most Common Adverse Reactions" section on page 9. For a full tabulated list of adverse reactions please refer to the SmPC in Appendix 1.

The following text describes the most important identified and potential risks associated with Nplate® administration, as well as relevant precautions that should be considered.

2.2 Identified Risks[1]

2.2.1 Increased bone marrow reticulin

Bone marrow reticulin is a non-specific finding that can be seen in ITP patients without exposure to thrombopoietic agents such as Nplate®. In a retrospective analysis of bone marrow from 40 patients with ITP who had not received thrombopoietic agents, bone marrow reticulin was present in approximately two thirds.[3]

Increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines.

In clinical studies, bone marrow abnormalities involving reticulin were reported in 3.7% of Nplate®-treated ITP patients. These adverse events were classified as: mild (1 case), moderate (3 cases), or severe (4 cases). Two additional cases were not reported as an adverse event.
Increased bone marrow reticulin may be suggested by morphological changes in the peripheral blood cells and can be detected through bone marrow biopsy. Therefore, examinations for cellular morphological abnormalities using peripheral blood smear and complete blood count (CBC) prior to and during treatment with Nplate® are recommended.

Please see SmPC in Appendix 1.

If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of Nplate® should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for bone marrow reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of Nplate® and alternative ITP treatment options should be re-assessed.

The natural course of a reticulin increase in the bone marrow is not known.

2.2.2 Progression of existing Myelodysplastic Syndromes (MDS)

A positive benefit/risk for Nplate® is only established for the treatment of thrombocytopenia associated with chronic ITP and Nplate® must not be used in other clinical conditions associated with thrombocytopenia.

The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. A bone marrow aspirate and biopsy should normally have been done over the course of the disease and treatment, particularly in patients over 60 years of age, for those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

In clinical studies of treatment with Nplate® in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myelogenous leukaemia (AML) were reported. Based on available data from a randomised trial, there were numerically more subjects in the Nplate® arm with disease progression to AML (placebo 2/72, Nplate® 9/147) and with an increase in circulating blasts to greater than 10% (placebo 3/72, Nplate® 25/147). The randomisation was 2:1 (Nplate®:placebo). Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML compared to lower risk MDS. Overall survival and AML free survival were similar to placebo. More haemorrhagic deaths were reported in the placebo arm. A reduction in the risk for clinically significant bleeding events and platelet transfusion events was seen with Nplate® treatment.

Nplate® must not be used for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.

2.2.3 Thrombocytosis

Based on an analysis of all adult ITP patients receiving Nplate® in 4 controlled and 5 uncontrolled clinical studies, 3 events of thrombocytosis were reported, n = 271. No clinical sequelae were reported in association with the elevated platelet counts in any of the 3 subjects.

Nplate® romiplostim

Please see SmPC in Appendix 1.

Since Nplate® acts by increasing platelet counts in a dose-dependent manner, Nplate® dosing instructions should be carefully followed, including instructions for withholding the dose in case of elevated platelet counts and additional therapies as deemed necessary.

2.2.4 Reoccurrence of thrombocytopenia after cessation of treatment

Due to increased platelet consumption in ITP, thrombocytopenia is likely to reoccur upon discontinuation of Nplate®.

Based on an analysis of all adult ITP patients receiving Nplate® in 4 controlled and 5 uncontrolled clinical studies, 4 events of thrombocytopenia after cessation of treatment were reported, n = 271. In 3 of these 4 subjects, the decreases in platelet count were below the pretreatment baseline levels. These decreases were transient (i.e. resolved 1 to 14 days after onset), and in some cases treatment was required. The actual rate of thrombocytopenia after cessation of treatment is unknown, as many subjects in the clinical studies are still being treated with Nplate® in a long-term extension study (i.e. treatment has not been discontinued).

There is an increased risk of bleeding if Nplate® is discontinued in the presence of anticoagulants or antiplatelet 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, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

2.2.5 Thrombotic/thromboembolic complications

Platelet counts above the normal range present a risk for thrombotic/ thromboembolic complications. The incidence of thrombotic/thromboembolic events (TEEs) observed in clinical studies with ITP patients was 6.0% with Nplate® and 3.6% with placebo. Limited data are available on the background incidence/prevalence of thrombotic events in the ITP population.

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

Cases of TEEs, including portal vein thrombosis, have been reported in patients with chronic liver disease receiving TPO agonists. Nplate® should be used with caution in these populations (see section 1.4.3).

The dose adjustment guidelines provided in the SmPC should be followed to avoid platelet counts above the normal range.

Nplate® romiplostim

Please see SmPC in Appendix 1.

2.2.6 Identified risk of medication errors

Nplate® is a highly potent peptibody administered subcutaneously as a low volume dose. Medication errors may occur because Nplate® is administered in small volumes, and small differences in dose may have large effects on platelet counts. Healthcare professionals should pay special attention to accurate calculation of the dose of Nplate®, transcription of the medication order dosing instructions and reconstitution of Nplate® to minimise the risk of medication errors~~,~~ , (including overdose, and underdose)~~.~~ which may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications or in lower than expected platelet counts and associated bleeding.

Please refer to the section on Posology for instructions on how to store, reconstitute the product, calculate the dose required, and adjust dose on the basis of routine platelet count monitoring.

2.~~3~~2.~~3~~6.1 Minimising medication errors for patients self-administering Nplate®

After training in reconstitution and injection techniques by the HCP, Nplate® may be self-administered (away from a hospital setting). Patients who are eligible for self-injecting Nplate® (see section 1.3) should still return to their HCP every 4 weeks to have their platelet counts monitored. It is crucial that patients are trained to understand the importance of storing, reconstituting the product correctly and injecting the correct dose. Training and detailed instructions are available for the HCP and patients. A training (demonstration) kit is also available for physicians to train the patient to self-administer Nplate®.

In addition to routine platelet count monitoring, the 4-weekly visit to an HCP also provides an opportunity for a patient to express any issues/concerns with self-administration.

After the first 4 weeks of self-administration, the patient should be supervised while reconstituting and administering Nplate, to confirm the ability to administer Nplate correctly. Only patients who demonstrate the ability to reconstitute and self-administer Nplate are allowed to continue doing so.

2.3 Potential Risks[1]

Please see SmPC in Appendix 1.

2.3.1 Neutralising antibodies that cross-react with eTPO

As with all therapeutic proteins, there is a potential for immunogenicity. Antibodies to Nplate® may neutralise the activity of Nplate®. Antibodies to Nplate® that cross-react with endogenous thrombopoetin (eTPO) may neutralise the activity of Nplate® and eTPO and therefore induce a worsened thrombocytopenia.

In clinical studies, antibodies to Nplate® were examined. Of the adult ITP patients in clinical studies receiving Nplate®, 2 patients (0.4%) developed antibodies capable of neutralising the activity of Nplate® but these antibodies did not cross-react to eTPO. Approximately 4 months later, both patients tested negative for neutralising antibodies to Nplate®.

If formation of neutralising antibodies is suspected, contact the local representative of the Marketing Authorisation Holder at [**INCLUDE COUNTRY-SPECIFIC CONTACT DETAILS HERE**] for free antibody testing.

2.3.2 Potential consequences of off-label use where risk-benefit has not been adequately studied

The risk-benefit profile of Nplate® for the treatment of thrombocytopenia in non-ITP patient populations has not been established. Nplate® is not indicated for the treatment of thrombocytopenia caused by conditions other than ITP in adult patients. It is also important to note that risk-benefit for the treatment of paediatric ITP has not been established.

2.4 Most Common Adverse Reactions[1]

Frequencies are defined as: Very common (≥ 1/10) and Common (≥ 1/100 to < 1/10). Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

MOST COMMON ADVERSE REACTIONS

MedDRA system organ class	Very common	Common
Blood and lymphatic system disorders		Bone marrow disorder, thrombocytopenia
Gastrointestinal disorders		Nausea, diarrhea, abdominal pain, constipation, dyspepsia
General disorders and administration site conditions		Fatigue, oedema peripheral, influenza like illness, pain, asthenia, pyrexia,

Please see SmPC in Appendix 1.

		chills, injection site reaction
Injury, poisoning and procedural complications		Contusion
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, muscle spasms, pain in extremity, back pain, bone pain
Nervous system disorders	Headache	Dizziness, migraine, paraesthesia
Psychiatric disorders		Insomnia
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism
Skin and subcutaneous tissue disorders		Pruritus, ecchymosis, rash
Vascular disorders		Flushing

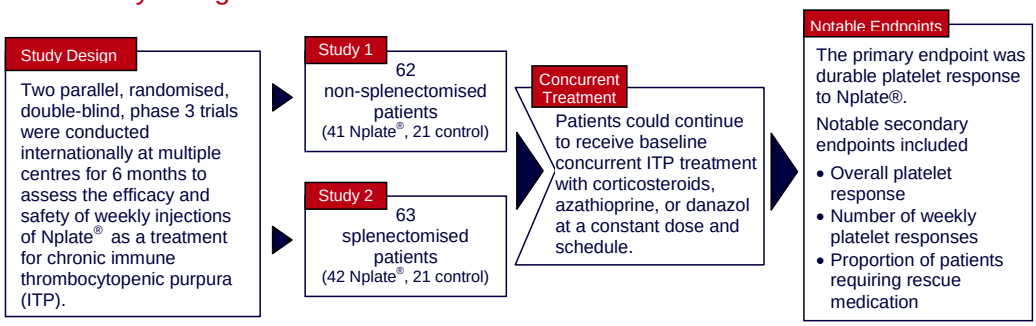
2.5 Bleeding Events[1]

- No significant effect on overall bleeding rates was observed between the Nplate® and placebo groups.
- An inverse relationship between bleeding events and platelet counts was observed across the entire ITP clinical programme.
  - All clinically significant (≥ grade 3; severe) bleeding events occurred at platelet counts < 30 x 10^9/L.
  - All bleeding events ≥ grade 2 (moderate) occurred at platelet counts < 50 x 10^9/L.
- Nine reports of clinically significant bleeding events occurred in the two studies: five (6.0%) Nplate® patients, vs four (9.8%) controls.
- Bleeding events ≥ grade 2 occurred in 15% of Nplate® patients, vs 34% of controls.

Please see SmPC in Appendix 1.

3. Clinical Experience

3.1 Study Design – Phase III[4]



3.2 Endpoint Definitions[4]

- A durable platelet response (primary efficacy measure) was defined as weekly platelet responses during at least 6 of the last 8 weeks of treatment in the 24-week study, without requiring rescue medication at any time during the study.
  - A weekly platelet response was defined as a platelet count ≥ 50 x 10^9/L at a weekly study visit.
  - A transient platelet response was defined as four or more weekly platelet responses without a durable platelet response from week 2 to week 25.
- Overall platelet response was defined as durable plus transient rates of platelet response.
- The proportion of patients needing rescue medications:
  - Rescue medication was defined as an increased dose of concurrent ITP drug or the use of any new drug to increase platelet counts.

Nplate® romiplostim

Please see SmPC in Appendix 1.

3.3 Clinical Response[4]

Key Efficacy Results in Study 20030212 (ITP patients who have not undergone splenectomy)

Endpoint	Placebo (N=21)	Romiplostim (N=41)	*p* value
Primary endpoint			
Durable platelet response[a]	1 (4.8%)	25 (61.0%)	< 0.0001
Incidence rate (95% CI)	(0.1%; 23.8%)	(44.5%; 75.8%)	
Key secondary endpoints			
Overall platelet response[b]	3 (14.3%)	36 (87.8%)	< 0.0001
Incidence rate (95% CI)	(3.0%; 36.3%)	(73.8%; 95.5%)	

a: From Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy. b: From analysis of variance, or CMH based on rank.

Key Efficacy Results in Study 20030105 (ITP patients refractory to splenectomy)

Endpoint	Placebo (N=21)	Romiplostim (N=42)	*p* value
Primary endpoint			
Durable platelet response[a]	0 (0%)	16 (38.1%)	0.0013
Incidence rate (95% CI)	(0%; 16.1%)	(23.6%; 54.4%)	
Key secondary endpoints			
Overall platelet response[b]	0 (0%)	33 (78.6%)	< 0.0001
Incidence rate (95% CI)	(0%; 16.1%)	(63.2%; 89.7%)	

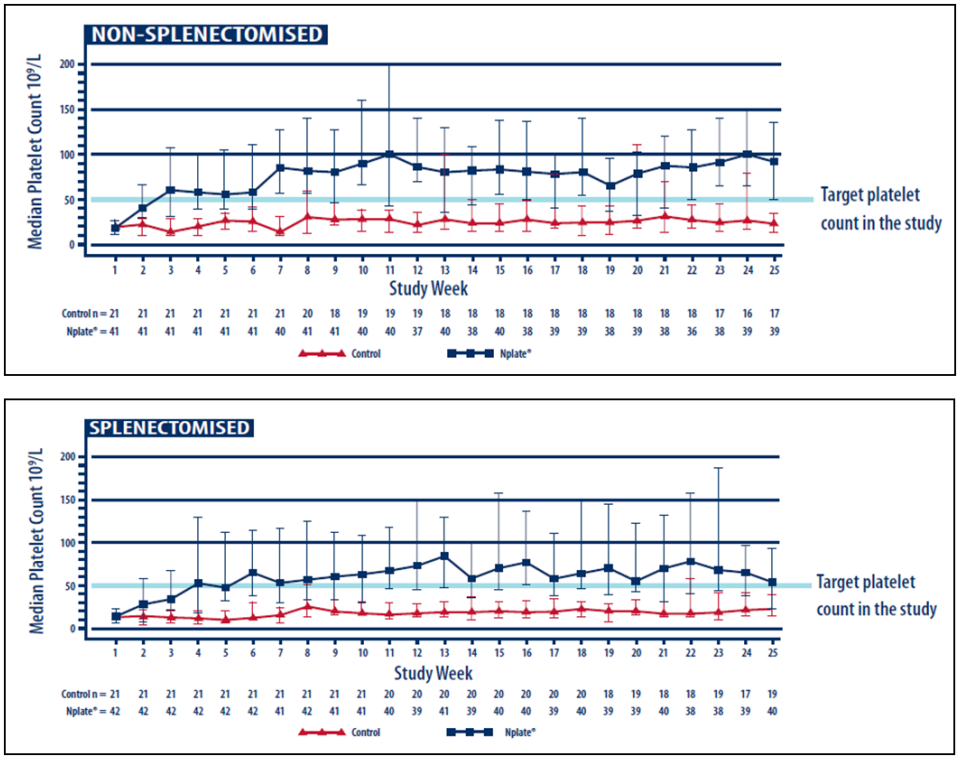
a: From Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy. b: From analysis of variance, or CMH based on rank.

Overall, 50% to 70% of Nplate® patients maintained target platelet levels

- Platelet counts ≥ 50 x 10^9/L were maintained in 50% to 70% of Nplate® patients during the 6 months of the study.
  - — In the control group, 0 to 7% of patients achieved a platelet count response.

Please see SmPC in Appendix 1.

MEDIAN PLATELET COUNTS THROUGHOUT THE 6-MONTH, PHASE 3 TRIALS*[4]



*Median weekly platelet count includes all patients, even those receiving rescue medication. Error bars indicate the range from the first to third quartiles.
Light-blue line indicates target platelet count in the study of 50 x 10^9/L.
Adapted from Kuter, et al [4]. The week numbers on the x-axis indicate the start of the study week

Secondary endpoint: Patients reduced or discontinued concurrent ITP therapy — 87% of Nplate® vs 38% placebo

Secondary endpoint: Use of rescue medication — 22% of Nplate® vs 60% placebo

Target platelet count rapidly achieved

- 50% of patients treated with Nplate® reached target platelet count (median platelet count of 50 x 10^9/L) within 2 to 3 weeks of initiating Nplate®.

Nplate® romiplostim

Please see SmPC in Appendix 1.

4. Posology and Reconstitution

4.1 Posology[1]

Treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Nplate® should be administered once weekly as a subcutaneous injection.

4.1.1 Initial dose

The initial dose of Nplate® is 1 µg/kg based on actual body weight.

4.1.2 Dose adjustments

A subject's actual body weight at initiation of therapy should be used to calculate dose. The once weekly dose of Nplate® should be increased by increments of 1 µg/kg until the patient achieves a platelet count ≥ 50 x 10^9/L. Platelet counts should be assessed weekly until a stable platelet count (≥ 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed every 4 weeks thereafter. A maximum once weekly dose of 10 µg/kg should not be exceeded.

Comment [T.O.1]: Changes made for consistency with QRD template changes made to the Product Information

Adjust the dose as follows:

Platelet count (x 10^9/L)	Action
< 50	Increase once weekly dose by 1 µg/kg
> 150 for two consecutive weeks	Decrease once weekly dose by 1 µg/kg
> 250	Do not administer, continue to assess the platelet count weekly After the platelet count has fallen to < 150 x 10^9/L, resume dosing with once weekly dose reduced by 1 µg/kg

Due to the interindividual variable platelet response, in some patients platelet count may abruptly fall below 50 x 10^9/L after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction (200 x 10^9/L) and treatment interruption (400 x 10^9/L) may be considered according to medical judgement.

Nplate® romiplostim

Please see SmPC in Appendix 1.

A loss of response or failure to maintain a platelet response with Nplate® within the recommended dosing range should prompt a search for causative factors (see section 4.4 of the Nplate® SmPC, “Loss of response to romiplostim”).

4.1.3 Dose calculation

Initial or subsequent once-weekly dose:	Weight* in kg x dose in µg/kg = Individual patient dose in µg
Volume to administer:	Dose in µg x $\frac{1\text{mL}}{500\ \mu\text{g}}$ = Amount to inject in mL
Example:	75 kg patient is initiated at 1 µg/kg of Nplate®. The individual patient dose = 75 kg x 1 µg/kg = 75 µg The corresponding amount of Nplate® solution to inject = 75 µg x $\frac{1\text{mL}}{500\ \mu\text{g}}$ = 0.15mL
*Actual body weight at initiation of treatment should always be used when calculating dose of Nplate®. Future dose adjustments are based on changes in platelet counts only and made in 1 µg/kg increments.	

- An Nplate® dosing calculator is available to aid in calculating dosages for individual patients (see Appendix 3).

4.2 Reconstitution[1]

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

Caution should be used during preparation of Nplate in calculating the dose and reconstitution with the correct volume of sterile water for injection. Special care should be taken to ensure that the appropriate volume of Nplate is withdrawn from the vial for subcutaneous administration (see sections 2.2.6).

4.2.1 Method of administration

Nplate® is available:

- on its own as a powder for solution for injection

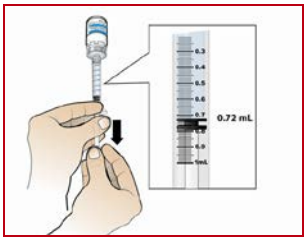
Please see SmPC in Appendix 1.

- as a complete reconstitution pack including Nplate® powder for solution for injection and a pre-filled syringe with sterile water for injection.

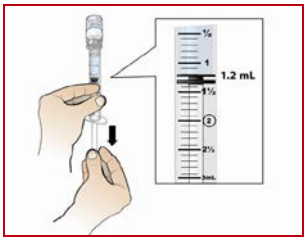
The method of administration is the same for both presentations. A very high level summary of the method of administration is as follows (further details are provided in the SmPCs (Appendix 1) / PILs (Appendix 2)). Please be aware there is a very detailed “Instructions for Use” provided at the end of the Patient Information Leaflet for patients considered suitable for self-administration. Physicians should ensure that patients are aware of this step-by-step instructions for use and keep it for future reference.

After reconstitution of the powder, Nplate® solution for injection is administered subcutaneously. The injection volume may be very small. **A syringe with graduations of 0.01 mL should be used. Warning: check your dose!**

- Nplate® is a sterile but unpreserved product and is intended for single use only. Nplate® should be reconstituted in accordance with good aseptic practice.
- Nplate® 500 µg powder for solution for injection should be reconstituted with 1.2 mL sterile water for injections, yielding a deliverable volume of 1 mL. An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered.

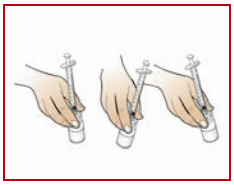


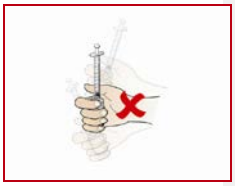
- Nplate® 250 µg powder for solution for injection should be reconstituted with 0.72 mL sterile water for injections, yielding a deliverable volume of 0.5 mL. An additional overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered.



- Sodium chloride solutions or bacteriostatic water should not be used when reconstituting the medicinal product.
- Water for injections should be injected into the vial. The vial contents may be swirled gently and inverted during dissolution.

  The vial should not be shaken or vigorously agitated. Generally, dissolution of Nplate® takes less than 2 minutes.





- Visually inspect the solution for particulate matter and discolouration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discolouration are observed.

Nplate® romiplostim

Please see SmPC in Appendix 1.

Warning: Before dosing, check that the reconstitution has been done correctly!

4.2.2 Storage of reconstituted Nplate®

- From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C or 24 hours in a refrigerator (2° to 8°C), protected from light.

The powder for solution for injection may be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C), protected from the light.

- Any unused product or waste material should be disposed of in accordance with local requirements.

Please see SmPC in Appendix 1.

5. References

1. Nplate [Summary of Product Characteristics]. Breda, The Netherlands: Amgen Europe B.V.

2. Kaushansky K. The molecular mechanisms that control thrombopoiesis. *J Clin Invest*. 2005;115:3339-3347.

3. Mufti G, Bagg A, Hasserjian R, et al. Bone marrow reticulin in patients with immune thrombocytopenic purpura. *Blood*. ASH Annual Meeting Abstracts, 2006;108: Abstract 3982.

4. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*. 2008;371:395-403.

6. Appendices

Appendix 1 — Nplate® Summary of Product Characteristics (SmPC)

Appendix 2 — Nplate® Patient Information Leaflet (PIL)

Appendix 3 — Nplate® Dose Calculator

Please see SmPC in Appendix 1.