

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Nplate 250 micrograms powder for solution for injection  
Nplate 500 micrograms powder for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Nplate 250 micrograms powder for solution for injection

Each vial contains 250 µg of romiplostim. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 µg of romiplostim (500 µg/ml). An additional overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered.

### Nplate 500 micrograms powder for solution for injection

Each vial contains 500 µg of romiplostim. After reconstitution, a deliverable volume of 1 ml solution contains 500 µg of romiplostim (500 µg/ml). An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered.

Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection)

The powder is white.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

### 4.2 Posology and method of administration

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

#### Posology

Nplate should be administered once weekly as a subcutaneous injection.

#### *Initial dose*

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

### 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 $\frac{1 \text{ ml}}{500 \text{ µg}}$ = Amount to inject in ml
Example:	75 kg patient is initiated at 1 µg/kg of romiplostim. The individual patient dose = 75 kg x 1 µg/kg = 75 µg The corresponding amount of Nplate solution to inject = $75 \text{ µg} \times \frac{1 \text{ ml}}{500 \text{ µg}} = 0.15 \text{ ml}$
*Actual body weight at initiation of treatment should always be used when calculating dose of romiplostim. Future dose adjustments are based on changes in platelet counts only and made in 1 µg/kg increments (see table below).	

### Dose adjustments

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

Adjust the dose as follows:

Platelet count (x 10 <sup>9</sup> /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 <sup>9</sup> /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  $50 \times 10^9/l$  after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction ( $200 \times 10^9/l$ ) and treatment interruption ( $400 \times 10^9/l$ ) may be considered according to medical judgement.

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

### Treatment discontinuation

Treatment with romiplostim should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of romiplostim therapy at the highest weekly dose of 10 µg/kg.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician, and in non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is likely upon discontinuation of treatment (see section 4.4).

### *Elderly patients ( $\geq 65$ years)*

No overall differences in safety or efficacy have been observed in patients  $< 65$  and  $\geq 65$  years of age (see section 5.1). 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.

### *Paediatric population*

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

### *Patients with hepatic Impairment*

Romiplostim should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score  $\geq 7$ ) unless the expected benefit outweighs the identified risk of portal venous thrombosis in patients with thrombocytopenia associated to hepatic insufficiency treated with thrombopoietin (TPO) agonists (see section 4.4).

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

### *Patients with renal impairment*

No formal clinical trials have been conducted in these patient populations. Nplate should be used with caution in these populations.

### Method of administration

For subcutaneous use.

After reconstitution of the powder, Nplate solution for injection is administered subcutaneously. The injection volume may be very small. 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 – a syringe with graduations of 0.01 ml should be used.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to *E. coli* derived proteins.

## **4.4 Special warnings and precautions for use**

### Reoccurrence of thrombocytopenia and bleeding after cessation of treatment

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with romiplostim. There is an increased risk of bleeding if romiplostim treatment 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 treatment with romiplostim. It is recommended that, if treatment with romiplostim 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.

### Increased bone marrow reticulin

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. Increased 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 romiplostim are recommended. See section 4.8 for information on the increases of reticulin observed in romiplostim clinical trials.

If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for 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 romiplostim and alternative ITP treatment options should be re-assessed.

### Thrombotic/thromboembolic complications

Platelet counts above the normal range present a risk for thrombotic/thromboembolic complications. The incidence of thrombotic/thromboembolic events observed in clinical trials was 6.0% with romiplostim and 3.6% with placebo. Caution should be used when administering romiplostim 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 thromboembolic events (TEEs), including portal vein thrombosis, have been reported in patients with chronic liver disease receiving romiplostim. Romiplostim should be used with caution in these populations. Dose adjustment guidelines should be followed (see section 4.2).

### Medication Errors

Medication errors including overdose and underdose have been reported in patients receiving Nplate, dose calculation and dose adjustment guidelines should be followed (see section 4.2).

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 sections 4.2, 4.4 and 4.9).

### Progression of existing Myelodysplastic Syndromes (MDS)

A positive benefit/risk for romiplostim is only established for the treatment of thrombocytopenia associated with chronic ITP and romiplostim 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 romiplostim in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported. In a randomized placebo-controlled trial in MDS subjects, treatment with romiplostim was prematurely stopped due to a numerical excess of disease progression to AML and an increase in circulating blasts greater than 10% in patients receiving romiplostim. 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.

Romiplostim 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.

#### Loss of response to romiplostim

A loss of response or failure to maintain a platelet response with romiplostim treatment within the recommended dosing range should prompt a search for causative factors, including immunogenicity (see section 4.8) and increased bone marrow reticulin (see above).

#### Effects of romiplostim on red and white blood cells

Alterations in red (decrease) and white (increase) blood cell parameters have been observed in non-clinical toxicology studies (rat and monkey) as well as in ITP patients. Concurrent anaemia and leucocytosis (within a 4-week window) may occur in patients regardless of splenectomy status, but have been seen more often in patients who have had a prior splenectomy. Monitoring of these parameters should be considered in patients treated with romiplostim.

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed. The potential interactions of romiplostim with co-administered medicinal products due to binding to plasma proteins remain unknown.

Medicinal products used in the treatment of ITP in combination with romiplostim in clinical trials included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining romiplostim with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Corticosteroids, danazol, and azathioprine use may be reduced or discontinued when given in combination with romiplostim (see section 5.1). Platelet counts should be monitored when reducing or discontinuing other ITP treatments in order to avoid platelet counts below the recommended range (see section 4.2).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no or limited amount of data from the use of romiplostim in pregnant women.

Studies in animals have shown that romiplostim crossed the placenta and increased foetal platelet counts. Post implantation loss and a slight increase in peri-natal pup mortality also occurred in animal studies (see section 5.3).

Romiplostim is not recommended during pregnancy and in women of childbearing potential not using contraception.

## Breast-feeding

It is unknown whether romiplostim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from romiplostim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

## Fertility

There is no data available on fertility.

### **4.7 Effects on ability to drive and use machines**

Nplate has moderate influence on the ability to drive and use machines. In clinical trials, mild to moderate, transient bouts of dizziness were experienced by some patients.

### **4.8 Undesirable effects**

#### Summary of the safety profile

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, the overall subject incidence of all adverse reactions for romiplostim-treated subjects was 91.5% (248/271). The mean duration of exposure to romiplostim in this study population was 50 weeks.

The most serious adverse reactions that may occur during Nplate treatment include: reoccurrence of thrombocytopenia and bleeding after cessation of treatment, increased bone marrow reticulin, thrombotic/thromboembolic complications, medication errors and progression of existing MDS to AML. The most common adverse reactions observed include hypersensitivity reactions (including cases of rash, urticaria and angioedema) and headache.

#### Tabulated list of adverse reactions

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Infections and infestations	Upper respiratory tract infection	Gastroenteritis	Influenza Localised infection Nasopharyngitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Multiple myeloma Myelofibrosis
Blood and lymphatic system disorders		Bone marrow disorder* Thrombocytopenia* Anaemia	Aplastic anaemia Bone marrow failure Leukocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal

<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Immune system disorder	Hypersensitivity**	Angioedema	
Metabolism and nutrition disorders			Alcohol intolerance Anorexia Decreased appetite Dehydration Gout
Psychiatric disorders		Insomnia	Depression Abnormal dreams
Nervous system disorders	Headache	Dizziness Migraine Paraesthesia	Clonus Dysgeusia Hypoaesthesia Hypogeusia Neuropathy peripheral Transverse sinus thrombosis
Eye disorders			Conjunctival haemorrhage Accommodation disorder Blindness Eye disorder Eye pruritus Lacrimation increased Papilloedema Visual disturbances
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Palpitations	Myocardial infarction Heart rate increased
Vascular disorders		Flushing	Deep vein thrombosis Hypotension Peripheral embolism Peripheral ischaemia Phlebitis Thrombophlebitis superficial Thrombosis Erythromelalgia
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration



<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Constipation Dyspepsia	Vomiting Rectal haemorrhage Breath odour Dysphagia Gastro-oesophageal reflux disease Haematochezia Mouth haemorrhage Stomach discomfort Stomatitis Tooth discolouration
Hepatobiliary disorders			Portal vein thrombosis Increase in transaminase
Skin and subcutaneous tissue disorders		Pruritus Echymosis Rash	Alopecia Photosensitivity reaction Acne Dermatitis contact Dry skin Eczema Erythema Exfoliative rash Hair growth abnormal Prurigo Purpura Rash papular Rash pruritic Skin nodule Skin odour abnormal Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle spasms Pain in extremity Back pain Bone pain	Muscle tightness Muscular weakness Shoulder pain Muscle twitching
Renal and urinary disorders			Protein urine present
Reproductive system and breast disorders			Vaginal haemorrhage
General disorders and administration site conditions		Fatigue Oedema peripheral Influenza like illness Pain Asthenia Pyrexia Chills Injection site reaction	Injection site haemorrhage Chest pain Irritability Malaise Face oedema Feeling hot Feeling jittery

MedDRA system organ class	Very common	Common	Uncommon
Investigations			Blood pressure increased Blood lactate dehydrogenase increased Body temperature increased Weight decreased Weight increased
Injury, poisoning and procedural complications		Contusion	

\* see section 4.4

\*\* Hypersensitivity reactions including cases of rash, urticaria, and angioedema

### Description of selected adverse reactions

In addition the reactions listed below have been deemed to be related to romiplostim treatment.

#### *Thrombocytosis*

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 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.

#### *Thrombocytopenia after cessation of treatment*

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 4 events of thrombocytopenia after cessation of treatment were reported, n = 271 (see section 4.4).

#### *Progression of existing Myelodysplastic Syndromes (MDS)*

In a randomized placebo-controlled trial in MDS subjects treatment with romiplostim was prematurely stopped due to a numerical increase in cases of MDS disease progression to AML and transient increases in blast cell counts in patients treated with romiplostim compared to 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 (see section 4.4). Overall survival was similar to placebo.

#### *Increased bone marrow reticulin*

In clinical trials, romiplostim treatment was discontinued in 4 of the 271 patients because of bone marrow reticulin deposition. In 6 additional patients reticulin was observed upon bone marrow biopsy (see section 4.4).

#### *Immunogenicity*

Clinical trials in adult ITP patients examined antibodies to romiplostim.

While 5.8% and 3.9% of the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 2 subjects (0.4%) were positive for neutralizing antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. Both subjects tested negative for neutralising antibodies to romiplostim at 4 months after the end of dosing. The incidence of pre-existing antibodies to romiplostim and TPO was 8.0% and 5.4%, respectively.

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact the local representative of the Marketing Authorisation Holder (see section 6 of the Package Leaflet) for antibody testing.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

#### **4.9 Overdose**

No adverse effects were seen in rats given a single dose of 1000 µg/kg or in monkeys after repeated administration of romiplostim at 500 µg/kg (100 or 50 times the maximum clinical dose of 10 µg/kg, respectively).

In the event of overdose, platelet counts may increase excessively and result in 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 (see sections 4.2 and 4.4).

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotics, other systemic hemostatics, ATC code: B02BX04

#### Mechanism of action

Romiplostim is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) 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 2 TPO receptor-binding domains.

Romiplostim has no amino acid sequence homology to endogenous TPO. In pre-clinical and clinical trials no anti-romiplostim antibodies cross reacted with endogenous TPO.

#### Clinical efficacy and safety

The safety and efficacy of romiplostim have been evaluated for up to 3 years of continuous treatment. In clinical trials, treatment with romiplostim resulted in dose-dependent increases in platelet count. Time to reach the maximum effect on platelet count is approximately 10-14 days, and is independent of the dose. After a single subcutaneous dose of 1 to 10 µg/kg romiplostim in ITP patients, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 week period and the response was variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 µg/kg of romiplostim were within the range of 50 to 450 x 10<sup>9</sup>/l for most patients. Of the 271 patients who received romiplostim in ITP clinical trials, 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.

### Results from pivotal placebo-controlled studies

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies in adults with ITP who had completed at least one treatment prior to study entry and are representative of the entire spectrum of such ITP patients.

Study S1 (212) evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior 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. Prior treatments included corticosteroids (90% of all patients), immunoglobulins (76%), rituximab (29%), cytotoxic therapies (21%), danazol (11%), and azathioprine (5%). Patients had a median platelet count of  $19 \times 10^9/l$  at study entry.

Study S2 (105) evaluated patients who were splenectomised 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. Prior treatments included corticosteroids (98% of all patients), immunoglobulins (97%), rituximab (71%), danazol (37%), cytotoxic therapies (68%), and azathioprine (24%). Patients had a median platelet count of  $14 \times 10^9/l$  at study entry.

Both studies were similarly designed. Patients ( $\geq 18$  years) were randomised in a 2:1 ratio to receive a starting dose of romiplostim  $1 \mu\text{g/kg}$  or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain ( $50$  to  $200 \times 10^9/l$ ) platelet counts. In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response. The median average weekly dose for splenectomised patients was  $3 \mu\text{g/kg}$  and for non-splenectomised patients was  $2 \mu\text{g/kg}$ .

A significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo in both studies. Following the first 4-weeks of study romiplostim maintained platelet counts  $\geq 50 \times 10^9/l$  in between 50% to 70% of patients during the 6 month treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able achieve a platelet count response during the 6 months of treatment. A summary of the key efficacy endpoints is presented below.

### Summary of key efficacy results from placebo-controlled studies

	Study 1 non-splenectomised patients		Study 2 splenectomised patients		Combined studies 1 & 2	
	romiplostim (n = 41)	Placebo (n = 21)	romiplostim (n = 42)	Placebo (n = 21)	romiplostim (n = 83)	Placebo (n = 42)
<b>No. (%) patients with durable platelet response<sup>a</sup></b>	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	
<b>No. (%) patients with overall platelet response<sup>b</sup></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	

	Study 1 non-splenectomised patients		Study 2 splenectomised patients		Combined studies 1 & 2	
	romiplostim (n = 41)	Placebo (n = 21)	romiplostim (n = 42)	Placebo (n = 21)	romiplostim (n = 83)	Placebo (n = 42)
<b>Mean no. weeks with platelet response<sup>c</sup></b>	15	1	12	0	14	1
(SD)	3.5	7.5	7.9	0.5	7.8	2.5
p-value	< 0.0001		< 0.0001		< 0.0001	
<b>No. (%) patients requiring rescue therapies<sup>d</sup></b>	8(20%)	13 (62%)	11 (26%)	12 (57%)	19 (23%)	25 (60%)
(95% CI)	(9%, 35%)	(38%, 82%)	(14%, 42%)	(34%, 78%)	(14%, 33%)	(43%, 74%)
p-value	0.001		0.0175		< 0.0001	
<b>No. (%) patients with durable platelet response with stable dose<sup>e</sup></b>	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	
<sup>a</sup> Durable platelet response was defined as weekly platelet count $\geq 50 \times 10^9/l$ for 6 or more times for study weeks 18-25 in the absence of rescue therapies any time during the treatment period. <sup>b</sup> Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count $\geq 50 \times 10^9/l$ 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 any rescue medicinal products. <sup>c</sup> Number of weeks with platelet response is defined as number of weeks with platelet counts $\geq 50 \times 10^9/l$ during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products. <sup>d</sup> Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medicinal products were not considered for durable platelet response. Rescue therapies allowed in the study were IVIG, platelet transfusions, anti-D immunoglobulin, and corticosteroids. <sup>e</sup> Stable dose defined as dose maintained within $\pm 1 \mu g/kg$ during the last 8 weeks of treatment.						

### Results of studies compared to standard of care (SOC) in non-splenectomised patients

Study S3 (131) was an open-label randomised 52 week trial in subjects who received romiplostim or medical standard of care (SOC) treatment. This study evaluated non-splenectomised patients with ITP and platelet counts  $< 50 \times 10^9/l$ . Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of  $3 \mu g/kg$ , and adjusted throughout the study within a range of  $1-10 \mu g/kg$  in order to maintain platelet counts between  $50$  and  $200 \times 10^9/l$ , 77 subjects received SOC treatment according to standard institutional practice or therapeutic guidelines.

The overall subject incidence rate of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35).

The overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61).

Of the 157 subjects randomised to the romiplostim group, three subjects did not receive romiplostim. Among the 154 subjects who received romiplostim, the total median exposure to romiplostim was 52.0 weeks and ranged from 2 to 53 weeks. The most frequently used weekly dose was between 3-5 µg/kg (25th-75th percentile respectively; median 3 µg/kg).

Of the 77 subjects randomised to the SOC group, two subjects did not receive any SOC. Among the 75 subjects who received at least one dose of SOC, the total median exposure to SOC was 51 weeks and ranged from 0.4 to 52 weeks.

#### *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 (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 (100%) splenectomised patients who were receiving romiplostim 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 placebo treated patients. Seventy-three percent of non-splenectomised patients receiving romiplostim 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 (see section 4.5).

#### *Bleeding events*

Across the entire ITP clinical programme an inverse relationship between bleeding events and platelet counts was observed. All clinically significant ( $\geq$  grade 3) bleeding events occurred at platelet counts  $< 30 \times 10^9/l$ . All bleeding events  $\geq$  grade 2 occurred at platelet counts  $< 50 \times 10^9/l$ . No statistically significant differences in the overall incidence of bleeding events were observed between Nplate and placebo treated patients.

In the two placebo-controlled studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] romiplostim, 4 [9.8%] placebo; Odds Ratio [romiplostim/placebo] = 0.59; 95% CI = (0.15, 2.31)). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with romiplostim and 34% of patients treated with placebo (Odds Ratio; [romiplostim/placebo] = 0.35; 95% CI = (0.14, 0.85)).

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Nplate in one or more subsets of the paediatric population in the treatment of immune thrombocytopenia (idiopathic thrombocytopenic purpura) (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

The pharmacokinetics of romiplostim involved target-mediated disposition, which is presumably mediated by TPO receptors on platelets and other cells of the thrombopoietic lineage such as megakaryocytes.

#### Absorption

After subcutaneous administration of 3 to 15 µg/kg romiplostim, maximum romiplostim serum levels in ITP patients were obtained after 7-50 hours (median 14 hours). The serum concentrations varied

among patients and did not correlate with the dose administered. Romiplostim serum levels appear inversely related to platelet counts.

### Distribution

The volume of distribution of romiplostim following intravenous administration of romiplostim decreased nonlinearly from 122, 78.8, to 48.2 ml/kg for intravenous doses of 0.3, 1.0 and 10 µg/kg, respectively in healthy subjects. This non-linear decrease in volume of distribution is in line with the (megakaryocyte and platelet) target-mediated binding of romiplostim, which may be saturated at the higher doses applied.

### Elimination

Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3.5 days). 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 trial, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 µg/kg).

### Special populations

Pharmacokinetics of romiplostim in patients with renal and hepatic impairment has not been investigated. Romiplostim pharmacokinetics appear not affected by age, weight and gender to a clinically significant extent.

## **5.3 Preclinical safety data**

Multiple dose romiplostim toxicology studies were conducted in rats for 4 weeks and in monkeys for up to 6 months. In general, effects observed during these studies were related to the thrombopoietic activity of romiplostim and were similar regardless of study duration. Injection site reactions were also related to romiplostim administration. Myelofibrosis has been observed in the bone marrow of rats at all tested dose levels. In these studies, myelofibrosis was not observed in animals after a 4-week post-treatment recovery period, indicating reversibility.

In 1-month rat and monkey toxicology studies, a mild decrease in red blood cell count, haematocrit and haemoglobin was observed. There was also a stimulatory effect on leukocyte production, as peripheral blood counts for neutrophils, lymphocytes, monocytes, and eosinophils were mildly increased. In the longer duration chronic monkey study, there was no effect on the erythroid and leukocytic lineages when romiplostim was administered for 6 months where the administration of romiplostim was decreased from thrice weekly to once weekly. Additionally, in the phase 3 pivotal studies, romiplostim did not affect the red blood cell and white blood cells lineages relative to placebo treated subjects.

Due to the formation of neutralising antibodies pharmacodynamic effects of romiplostim in rats were often decreasing at prolonged duration of administration. Toxicokinetic studies showed no interaction of the antibodies with the measured concentrations. Although high doses were tested in the animal studies, due to differences between the laboratory species and humans with regard to the sensitivity for the pharmacodynamic effect of romiplostim and the effect of neutralising antibodies, safety margins cannot be reliably estimated.

### Carcinogenesis

The carcinogenic potential of romiplostim has not been evaluated. Therefore, the risk of potential carcinogenicity of romiplostim in humans remains unknown.

## Reproductive toxicology

In all developmental studies neutralising antibodies were formed, which may have inhibited romiplostim effects. In embryo-foetal development studies in mice and rats, reductions in maternal body weight were found only in mice. In mice there was evidence of increased post-implantation loss. In a prenatal and postnatal development study in rats an increase of the duration of gestation and a slight increase in the incidence of peri-natal pup mortality was found. Romiplostim is known to cross the placental barrier in rats and may be transmitted from the mother to the developing foetus and stimulate foetal platelet production. Romiplostim had no observed effect on the fertility of rats.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol (E421)  
Sucrose  
L-histidine  
Hydrochloric acid (for pH adjustment)  
Polysorbate 20

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

### **6.3 Shelf life**

5 years.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for 24 hours at 2°C – 8°C, when protected from light and kept in the original vial.

From a microbiological point of view, the medicinal 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°C – 8°C), protected from light.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).  
Do not freeze.  
Store in the original carton in order to protect from light.  
May be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

5 ml vial (type 1 clear glass) with a stopper (chlorobutyl rubber), seal (aluminium) and a flip-off cap (polypropylene).

Carton containing 1 or 4 vials of romiplostim.

Not all pack sizes may be marketed.



## 6.6 Special precautions for disposal and other handling

Nplate is a sterile but unpreserved medicinal product and is intended for single use only. Nplate should be reconstituted in accordance with good aseptic practice.

### Nplate 250 micrograms powder for solution for injection

Nplate 250 micrograms 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 (see vial content table below).

### Nplate 500 micrograms powder for solution for injection

Nplate 500 micrograms 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 (see vial content table below).

Vial Content:

<b>Nplate single-use vial</b>	<b>Total vial content of romiplostim</b>		<b>Volume of sterile water for injection</b>		<b>Deliverable product and volume</b>	<b>Final concentration</b>
250 µg	375 µg	+	0.72 ml	=	250 µg in 0.5 ml	500 µg/ml
500 µg	625 µg	+	1.2 ml	=	500 µg in 1 ml	500 µg/ml

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 discoloration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discoloration are observed.

For the storage condition after reconstitution of the medicinal product see section 6.3.

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

## 7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/497/001  
EU/1/08/497/003  
EU/1/08/497/002  
EU/1/08/497/004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 4 February 2009

Date of latest renewal: 20 December 2013

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Nplate 250 micrograms powder and solvent for solution for injection  
Nplate 500 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nplate 250 micrograms powder and solvent for solution for injection

Each vial contains 250 µg of romiplostim. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 µg of romiplostim (500 µg/ml). An additional overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered.

Nplate 500 micrograms powder and solvent for solution for injection

Each vial contains 500 µg of romiplostim. After reconstitution, a deliverable volume of 1 ml solution contains 500 µg of romiplostim (500 µg/ml). An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered.

Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder for injection)

The powder is white.

The solvent is a clear colourless liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

### 4.2 Posology and method of administration

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

#### Posology

Nplate should be administered once weekly as a subcutaneous injection.

#### *Initial dose*

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

### Dose calculation

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

### Dose adjustments

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

Adjust the dose as follows:

Platelet count (x 10 <sup>9</sup> /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 <sup>9</sup> /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  $50 \times 10^9/l$  after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction ( $200 \times 10^9/l$ ) and treatment interruption ( $400 \times 10^9/l$ ) may be considered according to medical judgement.

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

### Treatment discontinuation

Treatment with romiplostim should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of romiplostim therapy at the highest weekly dose of 10 µg/kg.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician, and in non-splenectomised patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is likely upon discontinuation of treatment (see section 4.4).

### *Elderly patients (≥ 65 years)*

No overall differences in safety or efficacy have been observed in patients < 65 and ≥ 65 years of age (see section 5.1). 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.

### *Paediatric population*

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

### *Patients with hepatic Impairment*

Romiplostim 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 thrombopoietin (TPO) agonists (see section 4.4).

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

### *Patients with renal impairment*

No formal clinical trials have been conducted in these patient populations. Nplate should be used with caution in these populations.

### Method of administration

For subcutaneous use.

After reconstitution of the powder, Nplate solution for injection is administered subcutaneously. The injection volume may be very small. 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 – a syringe with graduations of 0.01 ml should be used.

Patients who have a stable platelet count ≥ 50 x 10<sup>9</sup>/l for at least 4 weeks without dose adjustment may, at the discretion of the supervising physician, self-administer Nplate solution for injection. Patients eligible for self-administration of Nplate should be trained in these procedures.

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

For instructions on reconstitution and administration of the medicinal product, see section 6.6.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to *E. coli* derived proteins.

#### **4.4 Special warnings and precautions for use**

##### Reoccurrence of thrombocytopenia and bleeding after cessation of treatment

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with romiplostim. There is an increased risk of bleeding if romiplostim treatment 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 treatment with romiplostim. It is recommended that, if treatment with romiplostim 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.

##### Increased bone marrow reticulin

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. Increased 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 romiplostim are recommended. See section 4.8 for information on the increases of reticulin observed in romiplostim clinical trials.

If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for 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 romiplostim and alternative ITP treatment options should be re-assessed.

##### Thrombotic/thromboembolic complications

Platelet counts above the normal range present a risk for thrombotic/thromboembolic complications. The incidence of thrombotic/thromboembolic events observed in clinical trials was 6.0% with romiplostim and 3.6% with placebo. Caution should be used when administering romiplostim 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 thromboembolic events (TEEs), including portal vein thrombosis, have been reported in patients with chronic liver disease receiving romiplostim. Romiplostim should be used with caution in these populations. Dose adjustment guidelines should be followed (see section 4.2).

##### Medication Errors

Medication errors including overdose and underdose have been reported in patients receiving Nplate, dose calculation and dose adjustment guidelines should be followed (see section 4.2).

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 sections 4.2, 4.4 and 4.9).

### Progression of existing Myelodysplastic Syndromes (MDS)

A positive benefit/risk for romiplostim is only established for the treatment of thrombocytopenia associated with chronic ITP and romiplostim 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 romiplostim in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported. In a randomized placebo-controlled trial in MDS subjects, treatment with romiplostim was prematurely stopped due to a numerical excess of disease progression to AML and an increase in circulating blasts greater than 10% in patients receiving romiplostim. 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.

Romiplostim 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.

### Loss of response to romiplostim

A loss of response or failure to maintain a platelet response with romiplostim treatment within the recommended dosing range should prompt a search for causative factors, including immunogenicity (see section 4.8) and increased bone marrow reticulin (see above).

### Effects of romiplostim on red and white blood cells

Alterations in red (decrease) and white (increase) blood cell parameters have been observed in non-clinical toxicology studies (rat and monkey) as well as in ITP patients. Concurrent anaemia and leucocytosis (within a 4-week window) may occur in patients regardless of splenectomy status, but have been seen more often in patients who have had a prior splenectomy. Monitoring of these parameters should be considered in patients treated with romiplostim.

## **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed. The potential interactions of romiplostim with co-administered medicinal products due to binding to plasma proteins remain unknown.

Medicinal products used in the treatment of ITP in combination with romiplostim in clinical trials included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining romiplostim with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Corticosteroids, danazol, and azathioprine use may be reduced or discontinued when given in combination with romiplostim (see section 5.1). Platelet counts should be monitored when reducing or discontinuing other ITP treatments in order to avoid platelet counts below the recommended range (see section 4.2).

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

There are no or limited amount of data from the use of romiplostim in pregnant women.

Studies in animals have shown that romiplostim crossed the placenta and increased foetal platelet counts. Post implantation loss and a slight increase in peri-natal pup mortality also occurred in animal studies (see section 5.3).

Romiplostim is not recommended during pregnancy and in women of childbearing potential not using contraception.

### Breast-feeding

It is unknown whether romiplostim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from romiplostim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

### Fertility

There is no data available on fertility.

## 4.7 Effects on ability to drive and use machines

Nplate has moderate influence on the ability to drive and use machines. In clinical trials, mild to moderate, transient bouts of dizziness were experienced by some patients.

## 4.8 Undesirable effects

### Summary of the safety profile

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, the overall subject incidence of all adverse reactions for romiplostim-treated subjects was 91.5% (248/271). The mean duration of exposure to romiplostim in this study population was 50 weeks.

The most serious adverse reactions that may occur during Nplate treatment include: reoccurrence of thrombocytopenia and bleeding after cessation of treatment, increased bone marrow reticulin, thrombotic/thromboembolic complications, medication errors and progression of existing MDS to AML. The most common adverse reactions observed include hypersensitivity reactions (including cases of rash, urticaria and angioedema) and headache.

### Tabulated list of adverse reactions

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Infections and infestations	Upper respiratory tract infection	Gastroenteritis	Influenza Localised infection Nasopharyngitis



<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Multiple myeloma Myelofibrosis
Blood and lymphatic system disorders		Bone marrow disorder* Thrombocytopenia* Anaemia	Aplastic anaemia Bone marrow failure Leukocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal
Immune system disorder	Hypersensitivity**	Angioedema	
Metabolism and nutrition disorders			Alcohol intolerance Anorexia Decreased appetite Dehydration Gout
Psychiatric disorders		Insomnia	Depression Abnormal dreams
Nervous system disorders	Headache	Dizziness Migraine Paraesthesia	Clonus Dysgeusia Hypoesthesia Hypogeusia Neuropathy peripheral Transverse sinus thrombosis
Eye disorders			Conjunctival haemorrhage Accommodation disorder Blindness Eye disorder Eye pruritus Lacrimation increased Papilloedema Visual disturbances
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Palpitations	Myocardial infarction Heart rate increased
Vascular disorders		Flushing	Deep vein thrombosis Hypotension Peripheral embolism Peripheral ischaemia Phlebitis Thrombophlebitis superficial Thrombosis Erythromelalgia
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration

<b>MedDRA system organ class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Constipation Dyspepsia	Vomiting Rectal haemorrhage Breath odour Dysphagia Gastro-oesophageal reflux disease Haematochezia Mouth haemorrhage Stomach discomfort Stomatitis Tooth discolouration
Hepatobiliary disorders			Portal vein thrombosis Increase in transaminase
Skin and subcutaneous tissue disorders		Pruritus Ecchymosis Rash	Alopecia Photosensitivity reaction Acne Dermatitis contact Dry skin Eczema Erythema Exfoliative rash Hair growth abnormal Prurigo Purpura Rash papular Rash pruritic Skin nodule Skin odour abnormal Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle spasms Pain in extremity Back pain Bone pain	Muscle tightness Muscular weakness Shoulder pain Muscle twitching
Renal and urinary disorders			Protein urine present
Reproductive system and breast disorders			Vaginal haemorrhage
General disorders and administration site conditions		Fatigue Oedema peripheral Influenza like illness Pain Asthenia Pyrexia Chills Injection site reaction	Injection site haemorrhage Chest pain Irritability Malaise Face oedema Feeling hot Feeling jittery
Investigations			Blood pressure increased Blood lactate dehydrogenase increased Body temperature increased Weight decreased Weight increased

MedDRA system organ class	Very common	Common	Uncommon
Injury, poisoning and procedural complications		Contusion	

\* see section 4.4

\*\* Hypersensitivity reactions including cases of rash, urticaria, and angioedema

#### Description of selected adverse reactions

In addition the reactions listed below have been deemed to be related to romiplostim treatment.

##### *Thrombocytosis*

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 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.

##### *Thrombocytopenia after cessation of treatment*

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 4 events of thrombocytopenia after cessation of treatment were reported, n = 271 (see section 4.4).

##### *Progression of existing Myelodysplastic Syndromes (MDS)*

In a randomized placebo-controlled trial in MDS subjects treatment with romiplostim was prematurely stopped due to a numerical increase in cases of MDS disease progression to AML and transient increases in blast cell counts in patients treated with romiplostim compared to 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 (see section 4.4). Overall survival was similar to placebo.

##### *Increased bone marrow reticulín*

In clinical trials, romiplostim treatment was discontinued in 4 of the 271 patients because of bone marrow reticulín deposition. In 6 additional patients reticulín was observed upon bone marrow biopsy (see section 4.4).

##### *Immunogenicity*

Clinical trials in adult ITP patients examined antibodies to romiplostim.

While 5.8% and 3.9% of the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 2 subjects (0.4%) were positive for neutralizing antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. Both subjects tested negative for neutralising antibodies to romiplostim at 4 months after the end of dosing. The incidence of pre-existing antibodies to romiplostim and TPO was 8.0% and 5.4%, respectively.

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact the local representative of the Marketing Authorisation Holder (see section 6 of the Package Leaflet) for antibody testing.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## 4.9 Overdose

No adverse effects were seen in rats given a single dose of 1000 µg/kg or in monkeys after repeated administration of romiplostim at 500 µg/kg (100 or 50 times the maximum clinical dose of 10 µg/kg, respectively).

In the event of overdose, platelet counts may increase excessively and result in 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 (see sections 4.2 and 4.4).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihæmorrhagics, other systemic hemostatics, ATC code: B02BX04

#### Mechanism of action

Romiplostim is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) 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 2 TPO receptor-binding domains.

Romiplostim has no amino acid sequence homology to endogenous TPO. In pre-clinical and clinical trials no anti-romiplostim antibodies cross reacted with endogenous TPO.

#### Clinical efficacy and safety

The safety and efficacy of romiplostim have been evaluated for up to 3 years of continuous treatment. In clinical trials, treatment with romiplostim resulted in dose-dependent increases in platelet count. Time to reach the maximum effect on platelet count is approximately 10-14 days, and is independent of the dose. After a single subcutaneous dose of 1 to 10 µg/kg romiplostim in ITP patients, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 week period and the response was variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 µg/kg of romiplostim were within the range of 50 to 450 x 10<sup>9</sup>/l for most patients. Of the 271 patients who received romiplostim in ITP clinical trials, 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.

#### *Results from pivotal placebo-controlled studies*

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies in adults with ITP who had completed at least one treatment prior to study entry and are representative of the entire spectrum of such ITP patients.

Study S1 (212) evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior 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. Prior treatments included corticosteroids (90% of all patients), immunoglobulins (76%), rituximab (29%), cytotoxic therapies (21%), danazol (11%), and azathioprine (5%). Patients had a median platelet count of 19 x 10<sup>9</sup>/l at study entry.

Study S2 (105) evaluated patients who were splenectomised 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. Prior treatments included corticosteroids (98% of all patients), immunoglobulins (97%), rituximab (71%), danazol (37%), cytotoxic therapies (68%), and azathioprine (24%). Patients had a median platelet count of  $14 \times 10^9/l$  at study entry.

Both studies were similarly designed. Patients ( $\geq 18$  years) were randomised in a 2:1 ratio to receive a starting dose of romiplostim  $1 \mu\text{g/kg}$  or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain ( $50$  to  $200 \times 10^9/l$ ) platelet counts. In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response. The median average weekly dose for splenectomised patients was  $3 \mu\text{g/kg}$  and for non-splenectomised patients was  $2 \mu\text{g/kg}$ .

A significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo in both studies. Following the first 4-weeks of study romiplostim maintained platelet counts  $\geq 50 \times 10^9/l$  in between 50% to 70% of patients during the 6 month treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able achieve a platelet count response during the 6 months of treatment. A summary of the key efficacy endpoints is presented below.

*Summary of key efficacy results from placebo-controlled studies*

	Study 1 non-splenectomised patients		Study 2 splenectomised patients		Combined studies 1 & 2	
	romiplostim (n = 41)	Placebo (n = 21)	romiplostim (n = 42)	Placebo (n = 21)	romiplostim (n = 83)	Placebo (n = 42)
<b>No. (%) patients with durable platelet response<sup>a</sup></b>	25 (61%)	1 (5%)	16 (38%)	0 (0%)	41 (50%)	1 (2%)
<sup>(95%)</sup> CI	(45%, 76%)	(0%, 24%)	(24%, 54%)	(0%, 16%)	(38%, 61%)	(0%, 13%)
p- value	< 0.0001		0.0013		< 0.0001	
<b>No. (%) patients with overall platelet response<sup>b</sup></b>	36 (88%)	3 (14%)	33 (79%)	0 (0%)	69 (83%)	3 (7%)
<sup>(95%)</sup> CI	(74%, 96%)	(3%, 36%)	(63%, 90%)	(0%, 16%)	(73%, 91%)	(2%, 20%)
p- value	< 0.0001		< 0.0001		< 0.0001	

	Study 1 non-splenectomised patients		Study 2 splenectomised patients		Combined studies 1 & 2	
	romiplostim (n = 41)	Placebo (n = 21)	romiplostim (n = 42)	Placebo (n = 21)	romiplostim (n = 83)	Placebo (n = 42)
<b>Mean no. weeks with platelet response<sup>c</sup></b>	15	1	12	0	14	1
(SD)	3.5	7.5	7.9	0.5	7.8	2.5
p- value	< 0.0001		< 0.0001		< 0.0001	
<b>No. (%) patients requiring rescue therapies<sup>d</sup></b>	8(20%)	13 (62%)	11 (26%)	12 (57%)	19 (23%)	25 (60%)
(95% CI)	(9%, 35%)	(38%, 82%)	(14%, 42%)	(34%, 78%)	(14%, 33%)	(43%, 74%)
p- value	0.001		0.0175		< 0.0001	
<b>No. (%) patients with durable platelet response with stable dose<sup>e</sup></b>	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	
<sup>a</sup> Durable platelet response was defined as weekly platelet count $\geq 50 \times 10^9/l$ for 6 or more times for study weeks 18-25 in the absence of rescue therapies any time during the treatment period. <sup>b</sup> Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count $\geq 50 \times 10^9/l$ 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 any rescue medicinal products. <sup>c</sup> Number of weeks with platelet response is defined as number of weeks with platelet counts $\geq 50 \times 10^9/l$ during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products. <sup>d</sup> Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medicinal products were not considered for durable platelet response. Rescue therapies allowed in the study were IVIG, platelet transfusions, anti-D immunoglobulin, and corticosteroids. <sup>e</sup> Stable dose defined as dose maintained within $\pm 1 \mu\text{g/kg}$ during the last 8 weeks of treatment.						

#### *Results of studies compared to standard of care (SOC) in non-splenectomised patients*

Study S3 (131) was an open-label randomised 52 week trial in subjects who received romiplostim or medical standard of care (SOC) treatment. This study evaluated non-splenectomised patients with ITP and platelet counts  $< 50 \times 10^9/l$ . Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of  $3 \mu\text{g/kg}$ , and adjusted throughout the study within a range of  $1-10 \mu\text{g/kg}$  in order to maintain platelet counts between  $50$  and  $200 \times 10^9/l$ , 77 subjects received SOC treatment according to standard institutional practice or therapeutic guidelines.

The overall subject incidence rate of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35).

The overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61).

Of the 157 subjects randomised to the romiplostim group, three subjects did not receive romiplostim. Among the 154 subjects who received romiplostim, the total median exposure to romiplostim was 52.0 weeks and ranged from 2 to 53 weeks. The most frequently used weekly dose was between 3-5 µg/kg (25th-75th percentile respectively; median 3 µg/kg).

Of the 77 subjects randomised to the SOC group, two subjects did not receive any SOC. Among the 75 subjects who received at least one dose of SOC, the total median exposure to SOC was 51 weeks and ranged from 0.4 to 52 weeks.

#### *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 (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 (100%) splenectomised patients who were receiving romiplostim 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 placebo treated patients. Seventy-three percent of non-splenectomised patients receiving romiplostim 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 (see section 4.5).

#### *Bleeding events*

Across the entire ITP clinical programme an inverse relationship between bleeding events and platelet counts was observed. All clinically significant ( $\geq$  grade 3) bleeding events occurred at platelet counts  $< 30 \times 10^9/l$ . All bleeding events  $\geq$  grade 2 occurred at platelet counts  $< 50 \times 10^9/l$ . No statistically significant differences in the overall incidence of bleeding events were observed between Nplate and placebo treated patients.

In the two placebo-controlled studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] romiplostim, 4 [9.8%] placebo; Odds Ratio [romiplostim/placebo] = 0.59; 95% CI = (0.15, 2.31)). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with romiplostim and 34% of patients treated with placebo (Odds Ratio; [romiplostim/placebo] = 0.35; 95% CI = (0.14, 0.85)).

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Nplate in one or more subsets of the paediatric population in the treatment of immune thrombocytopenia (idiopathic thrombocytopenic purpura) (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

The pharmacokinetics of romiplostim involved target-mediated disposition, which is presumably mediated by TPO receptors on platelets and other cells of the thrombopoietic lineage such as megakaryocytes.

## Absorption

After subcutaneous administration of 3 to 15 µg/kg romiplostim, maximum romiplostim serum levels in ITP patients were obtained after 7-50 hours (median 14 hours). The serum concentrations varied among patients and did not correlate with the dose administered. Romiplostim serum levels appear inversely related to platelet counts.

## Distribution

The volume of distribution of romiplostim following intravenous administration of romiplostim decreased nonlinearly from 122, 78.8, to 48.2 ml/kg for intravenous doses of 0.3, 1.0 and 10 µg/kg, respectively in healthy subjects. This non-linear decrease in volume of distribution is in line with the (megakaryocyte and platelet) target-mediated binding of romiplostim, which may be saturated at the higher doses applied.

## Elimination

Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3.5 days). 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 trial, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 µg/kg).

## Special populations

Pharmacokinetics of romiplostim in patients with renal and hepatic impairment has not been investigated. Romiplostim pharmacokinetics appear not affected by age, weight and gender to a clinically significant extent.

### **5.3 Preclinical safety data**

Multiple dose romiplostim toxicology studies were conducted in rats for 4 weeks and in monkeys for up to 6 months. In general, effects observed during these studies were related to the thrombopoietic activity of romiplostim and were similar regardless of study duration. Injection site reactions were also related to romiplostim administration. Myelofibrosis has been observed in the bone marrow of rats at all tested dose levels. In these studies, myelofibrosis was not observed in animals after a 4-week post-treatment recovery period, indicating reversibility.

In 1-month rat and monkey toxicology studies, a mild decrease in red blood cell count, haematocrit and haemoglobin was observed. There was also a stimulatory effect on leukocyte production, as peripheral blood counts for neutrophils, lymphocytes, monocytes, and eosinophils were mildly increased. In the longer duration chronic monkey study, there was no effect on the erythroid and leukocytic lineages when romiplostim was administered for 6 months where the administration of romiplostim was decreased from thrice weekly to once weekly. Additionally, in the phase 3 pivotal studies, romiplostim did not affect the red blood cell and white blood cells lineages relative to placebo treated subjects.

Due to the formation of neutralising antibodies pharmacodynamic effects of romiplostim in rats were often decreasing at prolonged duration of administration. Toxicokinetic studies showed no interaction of the antibodies with the measured concentrations. Although high doses were tested in the animal studies, due to differences between the laboratory species and humans with regard to the sensitivity for the pharmacodynamic effect of romiplostim and the effect of neutralising antibodies, safety margins cannot be reliably estimated.



## Carcinogenesis

The carcinogenic potential of romiplostim has not been evaluated. Therefore, the risk of potential carcinogenicity of romiplostim in humans remains unknown.

## Reproductive toxicology

In all developmental studies neutralising antibodies were formed, which may have inhibited romiplostim effects. In embryo-foetal development studies in mice and rats, reductions in maternal body weight were found only in mice. In mice there was evidence of increased post-implantation loss. In a prenatal and postnatal development study in rats an increase of the duration of gestation and a slight increase in the incidence of peri-natal pup mortality was found. Romiplostim is known to cross the placental barrier in rats and may be transmitted from the mother to the developing foetus and stimulate foetal platelet production. Romiplostim had no observed effect on the fertility of rats.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol (E421)  
Sucrose  
L-histidine  
Hydrochloric acid (for pH adjustment)  
Polysorbate 20

Solvent:  
Water for injections

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

### **6.3 Shelf life**

3 years.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for 24 hours at 2°C – 8°C, when protected from light and kept in the original vial.

From a microbiological point of view, the medicinal 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°C – 8°C), protected from light.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C – 8°C).  
Do not freeze.  
Store in the original carton in order to protect from light.  
May be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

### Powder:

5 ml vial (type 1 clear glass) with a stopper (chlorobutyl rubber), seal (aluminium) and a flip-off cap (polypropylene).

### Solvent:

Nplate 250 micrograms powder and solvent for solution for injection: Pre-filled syringe (type 1 clear glass with bromobutyl rubber plunger) containing 0.72 ml of water for injections for reconstitution.

Nplate 500 micrograms powder and solvent for solution for injection: Pre-filled syringe (type 1 clear glass with bromobutyl rubber plunger) containing 1.2 ml of water for injections for reconstitution.

### Pack size:

Nplate 250 micrograms powder and solvent for solution for injection:

Nplate is supplied as a 1 pack or multipack comprising 4 packs. Each pack contains:

1 vial of 250 micrograms romiplostim.

1 pre-filled syringe containing 0.72 ml of water for injections for reconstitution.

1 plunger rod for the pre-filled syringe.

1 sterile vial adapter.

1 sterile 1 ml Luer lock syringe.

1 sterile safety needle.

4 alcohol swabs.

Nplate 500 micrograms powder and solvent for solution for injection:

Nplate is supplied as a 1 pack or multipack comprising 4 packs. Each pack contains:

1 vial of 500 micrograms romiplostim.

1 pre-filled syringe containing 1.2 ml of water for injections for reconstitution.

1 plunger rod for the pre-filled syringe.

1 sterile vial adapter.

1 sterile 1 ml Luer lock syringe.

1 sterile safety needle.

4 alcohol swabs.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Nplate is a sterile but unpreserved medicinal product and is intended for single use only. Nplate should be reconstituted in accordance with good aseptic practice.

### Nplate 250 micrograms powder and solvent for solution for injection

Nplate 250 micrograms 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 (see vial content table below).

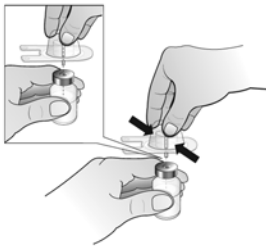

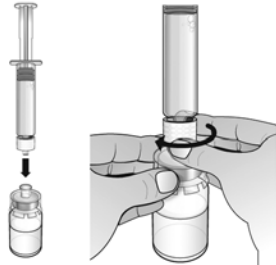
### Nplate 500 micrograms powder and solvent for solution for injection


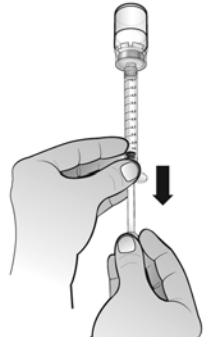
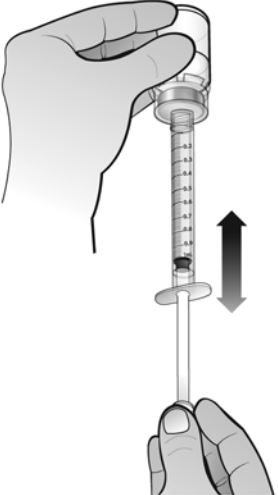
Nplate 500 micrograms powder for solution for injection should be reconstituted with 1.2 ml sterile water for injections, yielding a deliverable volume of 1 ml. An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered (see vial content table below).

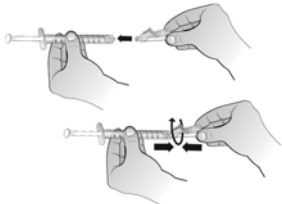

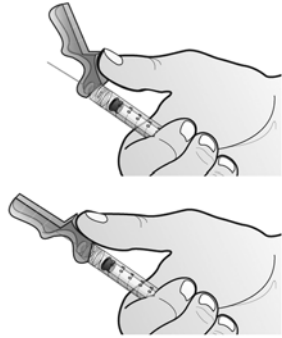
Vial Content:

Nplate single-use vial	Total vial content of romiplostim		Volume of sterile water for injection		Deliverable product and volume	Final concentration
250 µg	375 µg	+	0.72 ml	=	250 µg in 0.5 ml	500 µg/ml
500 µg	625 µg	+	1.2 ml	=	500 µg in 1 ml	500 µg/ml

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°C – 8°C), protected from light.

<p>1. Remove the plastic cap from Nplate powder vial and clean rubber stopper using the provided alcohol swab.</p>	
<p>2. Attach vial adapter to Nplate vial by peeling off <b>paper backing from vial adapter, keeping the vial adapter in its packaging</b>. Keeping the <b>vial on the bench</b>, push the vial adapter down onto the centre of the vial until it is firmly in place.</p> <p><b>Note: To prevent contamination of the product, do not touch the vial adapter spike or Luer lock.</b></p>	
<p>3. <b>Remove and discard vial adapter packaging.</b></p>	
<p>4. <b>Attach plunger rod to the pre-filled syringe of water for injections</b> by twisting the plunger rod clockwise onto the syringe plunger, until you feel a slight resistance.</p>	
<p>5. <b>Holding the pre-filled syringe of water for injections with one hand, bend the tip of the white plastic cover downward with your other hand. This will break the seal of the white plastic cover. Once the seal is broken, pull cover off to separate the grey rubber cap from the clear plastic tip on the syringe.</b></p>	
<p>6. <b>Keeping the vial on the bench, attach the pre-filled syringe of water for injections to vial adapter:</b> hold the outer edge of the vial adapter with one hand and twist the syringe tip clockwise onto the adapter with the other hand until you feel a slight resistance.</p>	

<p>7. <b><u>Very slowly and gently expel all water</u></b> into powder vial. Water should flow slowly onto powder. GENTLY swirl the vial until all of the powder has dissolved and the liquid in the vial is clear and colourless.</p> <p><b><u>Do not shake the vial</u></b></p> <p><b>Note: From a microbiological point of view, the product must be used immediately after reconstitution. If reconstituted product is not used immediately, the syringe should not be removed from the vial adapter to maintain microbiological integrity.</b></p>	 <p><b>Note:</b> This may take up to 2 minutes for the powder to completely dissolve.</p>
<p><b>Before continuing:</b></p> <p><b>Do</b> visually inspect the reconstituted solution for particulate matter and/or discoloration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discoloration are observed.</p> <p><b>Do</b> make sure solution is fully dissolved before removing syringe.</p>	
<p>8. Remove the empty pre-filled syringe from the vial adapter.</p>	
<p>9. <b>Remove 1 ml administration syringe from package. Attach the 1 ml syringe to vial adapter of reconstituted solution</b> by twisting the syringe tip onto the vial adapter until you feel a slight resistance.</p>	
<p>10. <b>Turn assembled syringe-vial unit upside down</b>, so the vial of reconstituted product is above the syringe. <b>Withdraw all</b> of the medicinal product solution into the administration syringe.</p> <p><b>Do</b> ensure that the plunger remains in the syringe.</p>	
<p>11. <b>Ensure the correct amount of solution</b> for the patient dose is in the administration syringe by injecting any excess solution back into the vial.</p> <p><b>Note: Remove all air bubbles from syringe to ensure precise solution amount is in syringe.</b></p>	

<p>12. <b>Twist off administration syringe from vial adapter.</b></p> <p><b>Attach safety needle</b> to the filled administration syringe by twisting needle <b>clockwise</b> into syringe Luer lock tip.</p>	
<p>13. Prepare injection site with a new alcohol swab. <b>Pull back on the pink safety cover</b> toward the syringe and away from the needle.</p> <p><b>Remove clear needle shield from prepared needle</b> by holding syringe in one hand and carefully pulling shield straight off with the other hand.</p>	
<p>14. <b>Administer subcutaneous injection</b> following local protocols and good aseptic technique.</p>	
<p>15. <b>After injecting, activate the pink safety cover</b> by pushing the cover forward using the same hand until you hear and/or feel it click/lock.</p>	
<p>16. <b>Immediately discard syringe and needle</b> into an approved Sharps Container.</p>	

For the storage condition after reconstitution of the product see section 6.3.

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

## 7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/497/005  
EU/1/08/497/006  
EU/1/08/497/007  
EU/1/08/497/008

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 4 February 2009

Date of latest renewal: 20 December 2013

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR  
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY  
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE  
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO  
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL  
PRODUCT**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

Amgen Inc  
One Amgen Center Drive  
Thousand Oaks, CA 91320  
USA

Amgen Manufacturing Limited  
State Road 31,  
Km 24.6,  
Juncos,  
Puerto Rico 00777-4060  
USA

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.  
Minervum 7061  
NL-4817 ZK Breda  
The Netherlands

Amgen Technology Ireland (ADL)  
Pottery Road  
Dun Laoghaire  
Co Dublin  
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.



## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

### **• Additional risk minimisation measures**

The MAH shall agree the details of the following educational tools with the National Competent Authorities and must implement such programme nationally.

#### **Dose calculator**

- Physicians involved in the prescribing of romiplostim are provided with a dosing calculator to simplify the calculation of the correct dose and guide to the correct reconstitution and administration procedures.

#### **Home Administration Training (HAT) pack**

- Physicians who express an interest in initiating self-administration for specific patients are provided with a HAT pack for those patients. The HAT pack includes materials for HCPs on how to select and train patients for self-administration of romiplostim; and for patients, in order to help them with the process of preparation and self-administration of the correct dose of romiplostim.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 250 micrograms powder for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 250 micrograms of romiplostim. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for injection.

1 vial.

4 vials.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/001  
EU/1/08/497/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Nplate 250

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

Nplate 250 µg powder for injection  
romiplostim  
SC

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

250 µg

**6. OTHER**

Amgen Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 500 micrograms powder for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 500 micrograms of romiplostim. After reconstitution, a deliverable volume of 1 ml solution contains 500 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for injection.

1 vial.

4 vials.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.

Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/002  
EU/1/08/497/004

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Nplate 500



**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION**

Nplate 500 µg powder for injection  
romiplostim  
SC

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

500 µg

**6. OTHER**

Amgen Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**RECONSTITUTION PACK INNER CARTON WITHOUT BLUE BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 250 micrograms powder and solvent for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 250 micrograms of romiplostim. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Powder: Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Component of a multipack, not to be sold separately.  
1 pack containing:  
1 vial of powder for solution for injection.  
1 pre-filled syringe containing 0.72 ml of solvent.  
1 plunger rod for pre-filled syringe.  
1 sterile vial adapter.  
1 sterile 1 ml Luer lock syringe.  
1 sterile safety needle.  
4 alcohol swabs.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/006 – 1 pack

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nplate 250

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**RECONSTITUTION PACK OUTER CARTON WITH BLUE BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 250 micrograms powder and solvent for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 250 micrograms of romiplostim. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Powder: Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 pack containing:  
Multipack: comprising 4 packs  
Each pack contains:  
1 vial of powder for solution for injection.  
1 pre-filled syringe containing 0.72 ml of solvent.  
1 plunger rod for pre-filled syringe.  
1 sterile vial adapter.  
1 sterile 1 ml Luer lock syringe.  
1 sterile safety needle.  
4 alcohol swabs.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/005 – 1 pack

EU/1/08/497/006 – 4 pack

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nplate 250

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**RECONSTITUTION PACK INNER CARTON WITHOUT BLUE BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 500 micrograms powder and solvent for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 500 micrograms of romiplostim. After reconstitution, a deliverable volume of 1 ml solution contains 500 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Powder: Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Component of a multipack, not to be sold separately.  
1 pack containing:  
1 vial of powder for solution for injection.  
1 pre-filled syringe containing 1.2 ml of solvent.  
1 plunger rod for pre-filled syringe.  
1 sterile vial adapter.  
1 sterile 1 ml Luer lock syringe.  
1 sterile safety needle.  
4 alcohol swabs.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/008 – 1 pack

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nplate 500

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**RECONSTITUTION PACK OUTER CARTON WITH BLUE BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Nplate 500 micrograms powder and solvent for solution for injection  
romiplostim

**2. STATEMENT OF ACTIVE SUBSTANCE**

Vial containing 500 micrograms of romiplostim. After reconstitution, a deliverable volume of 1 ml solution contains 500 micrograms of romiplostim (500 micrograms/ml).

**3. LIST OF EXCIPIENTS**

Powder: Mannitol (E421), sucrose, l-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 pack containing:  
Multipack: comprising 4 packs  
Each pack contains:  
1 vial of powder for solution for injection.  
1 pre-filled syringe containing 1.2 ml of solvent.  
1 plunger rod for pre-filled syringe.  
1 sterile vial adapter.  
1 sterile 1 ml Luer lock syringe.  
1 sterile safety needle.  
4 alcohol swabs.

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Subcutaneous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**



**8. EXPIRY DATE**

EXP

After reconstitution: 24 hours when stored at 25°C or in a refrigerator (2°C – 8°C) if kept in the original vial and protected from light.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Store in the original carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**12. MARKETING AUTHORISATION NUMBERS**

EU/1/08/497/007 – 1 pack

EU/1/08/497/008 – 4 pack

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Nplate 500

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**WATER FOR INJECTIONS LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for Nplate  
Water for injections

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

0.72 ml

1.2 ml

**6. OTHER**

For 250 µg kit

For 500 µg kit

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### **Nplate 250 micrograms powder for solution for injection** **Nplate 500 micrograms powder for solution for injection** Romiplostim

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Nplate is and what it is used for
2. What you need to know before you use Nplate
3. How to use Nplate
4. Possible side effects
5. How to store Nplate
6. Contents of the pack and other information

#### **1. What Nplate is and what it is used for**

Nplate's active ingredient is romiplostim, which is a protein used to treat low platelet counts in patients with immune (idiopathic) thrombocytopenic purpura (called ITP). ITP is a disease in which your body's immune system destroys its own platelets. Platelets are the cells in your blood that help seal cuts and form blood clots. Very low platelet counts can cause bruising and serious bleeding.

Nplate is used to treat adult patients (aged 18 years and over) who may or may not have had their spleen removed for chronic ITP and who have been previously treated with corticosteroids or immunoglobulins, where these treatments don't work.

Nplate works by stimulating the bone marrow (part of the bone which makes blood cells) to produce more platelets. This should help to prevent bruising and bleeding associated with ITP.

#### **2. What you need to know before you use Nplate**

##### **Do not use Nplate:**

- if you are allergic to romiplostim or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines that are produced by DNA technology using the micro-organism *Escherichia coli* (*E. coli*).

##### **Warnings and precautions**

- If you stop taking Nplate a low blood platelet count (thrombocytopenia) is likely to reoccur. If you stop taking Nplate your platelet count will have to be monitored, and your doctor will discuss appropriate precautions with you.
- If you are at risk of blood clots or if blood clots are common in your family. The risk of blood clotting may also be increased if you:
  - have liver problems;
  - are elderly ( $\geq 65$  years);

- are bedridden;
- have cancer;
- are taking the contraceptive pill or hormone replacement therapy;
- have recently had surgery or suffered an injury;
- are obese (overweight);
- are a smoker.

Talk to your doctor, pharmacist or nurse before using Nplate.

If you have very high blood platelet counts this may increase the risk of blood clotting. Your doctor will adjust your dose of Nplate to ensure that your platelet count does not become too high.

#### 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” and has been observed in Nplate clinical trials. It is not known if this may progress to a more severe form called “fibrosis.” Signs of bone marrow changes may show up as abnormalities in your blood tests. Your doctor will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate.

#### Worsening of blood cancers

Your doctor may decide to take a bone marrow biopsy if they decide it is necessary to ensure that you have ITP, and not another condition such as Myelodysplastic Syndrome (MDS). If you have MDS and receive Nplate you may have an increase in your blast cell counts and your MDS condition may worsen to become an acute myeloid leukaemia, which is a type of cancer of the blood.

#### Loss of response to romiplostim

If you experience a loss of response or failure to maintain a platelet response with romiplostim treatment, your doctor will investigate the reasons why including whether you are experiencing increased bone marrow fibres (reticulin) or have developed antibodies which neutralise romiplostim’s activity.

#### **Children and adolescents**

Nplate is not recommended for use in children below age 18.

#### **Other medicines and Nplate**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are also taking medicines which prevent blood clots (anticoagulants or antiplatelet therapy) there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking corticosteroids, danazol, and/or azathioprine, which you may be receiving to treat your ITP, these may be reduced or stopped when given together with Nplate.

#### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Nplate is not recommended for use if you are pregnant unless indicated by your doctor.

It is not known whether romiplostim is present in human milk. Nplate is not recommended for use if you are breast-feeding. A decision on whether to discontinue breast-feeding or discontinue therapy

with romiplostim should be made taking into account the benefit of breast-feeding to your child and the benefit of romiplostim therapy to you.

### **Driving and using machines**

You should speak with your doctor before driving or using machines, as some side effects (e.g., temporary bouts of dizziness) may impair your ability to do so safely.

### **3. How to use Nplate**

Nplate will be given under the direct supervision of your doctor, who will closely control the amount of Nplate given to you.

Nplate is administered once a week as an injection under the skin (subcutaneous).

Your initial dose is 1 microgram of Nplate per kilogram of your body weight once a week. Your doctor will tell you how much you must take. Nplate should be injected once per week in order to keep your platelet counts up. Your doctor will take regular blood samples to measure how your platelets are responding and may adjust your dose as necessary.

Once your platelet count is under control, your doctor will continue to regularly check your blood. Your dose may be adjusted further in order to maintain long-term control of your platelet count.

#### **If you use more Nplate than you should**

Your doctor will ensure that you receive the right amount of Nplate. If you have been given more Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may rise to very high levels and this may increase the risk of blood clotting. Therefore if your doctor suspects that you have been given more Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

#### **If you use less Nplate than you should**

Your doctor will ensure that you receive the right amount of Nplate. If you have been given less Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may become low and this may increase the risk of bleeding. Therefore if your doctor suspects that you have been given less Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

#### **If you forget to use Nplate**

If you have missed a dose of Nplate, your doctor will discuss with you when you should have your next dose.

#### **If you stop using Nplate**

If you stop using Nplate, your low blood platelet count (thrombocytopenia) is likely to reoccur. Your doctor will decide if you should stop using Nplate.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

##### **Very common: may affect more than 1 in 10 people**

- headache;
- allergic reaction;
- upper respiratory tract infection.

##### **Common: may affect up to 1 in 10 people**

- bone marrow disorder, including increased bone marrow fibres (reticulin);
- trouble sleeping (insomnia);
- dizziness;
- tingling or numbness of the hands or feet (paraesthesia);
- migraine;
- redness of the skin (flushing);
- blood clot in a lung artery (pulmonary embolism);
- nausea;
- diarrhoea;
- abdominal pain;
- indigestion (dyspepsia);
- constipation;
- itching of the skin (pruritis);
- bleeding under the skin (ecchymosis);
- bruising (contusion);
- rash;
- joint pain (arthralgia);
- muscles pain or weakness (myalgia);
- pain in your hands and feet;
- muscle spasm;
- back pain;
- bone pain;
- tiredness (fatigue);
- injection site reactions;
- swelling in the hands and feet (oedema peripheral);
- flu like symptoms (influenza like illness);
- pain;
- weakness (asthenia);
- fever (pyrexia);
- chills;
- contusion;
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema);
- gastroenteritis;
- palpitations.

##### **Common: may affect up to 1 in 10 people (may show up in blood or urine tests)**

- low blood platelet count (thrombocytopenia) and low blood platelet count (thrombocytopenia) after stopping Nplate;
- higher than normal platelet counts (thrombocytosis);
- anaemia.

##### **Uncommon: may affect up to 1 in 100 people**

- bone marrow failure; disorder of the bone marrow that causes scarring (myelofibrosis); enlarged spleen (splenomegaly); bleeding of the vagina (vaginal haemorrhage), bleeding in the

- rectum (rectal haemorrhage); bleeding mouth (mouth haemorrhage); injection site bleeding (injection site haemorrhage);
- heart attack (myocardial infarction); increased heart rate;
  - dizziness or a spinning sensation (vertigo);
  - problems with the eyes including: bleeding in the eye (conjunctival haemorrhage); difficulty focussing or blurred vision (accommodation disorder, papilloedema or eye disorder); blindness; itchy eye (eye pruritus); increased tears (lacrimation increased); or visual disturbances;
  - problems with the digestive system including: vomiting; bad breath (breath odour); difficulty swallowing (dysphagia); indigestion or heartburn (gastro-oesophageal reflux disease); blood in the stools (haematochezia); stomach discomfort; mouth ulcers or mouth blistering (stomatitis); discoloured teeth (tooth discolouration);
  - weight decreased; weight increased; intolerance of alcohol; loss of appetite (anorexia or decreased appetite); dehydration;
  - generally feeling unwell (malaise); chest pain; irritability; swelling of the face (face oedema); feeling hot; increased body temperature; feeling jittery;
  - influenza; localised infection; inflammation of the passages in the nose and throat (nasopharyngitis);
  - problems with the nose and throat including: cough; runny nose (rhinorrhoea); dry throat; shortness of breath or difficulty breathing (dyspnoea); nasal congestion; painful breathing (painful respiration)
  - painful swollen joints caused by uric acid (food breakdown product) (gout);
  - muscle tightness; muscular weakness; shoulder pain; muscle twitching;
  - problems with your nervous system including involuntary muscle contractions (clonus); distorted sense of taste (dysgeusia); decrease in sense of taste (hypogeusia); decreased feeling of sensitivity, especially in the skin (hypoesthesia); alteration in the nerve functions in the arms and legs (neuropathy peripheral); blood clot in the transverse sinus (transverse sinus thrombosis);
  - depression; abnormal dreams;
  - hair loss (alopecia); sensitivity to light (photosensitivity reaction); acne; allergic reaction in the skin upon contact with allergen (dermatitis contact); skin manifestation with rash and blisters (eczema); dry skin; redness of the skin (erythema); severe flaking or peeling rash (exfoliative rash); abnormal hair growth; thickening and itching of the skin due to repeated scratching (prurigo); bleeding beneath the surface of the skin or bruising under the skin (purpura); bumpy skin rash (rash papular); itchy skin rash (rash pruritic); generalised itchy rash (urticaria); bump on the skin (skin nodule); abnormal smell to the skin (skin odour abnormal);
  - problems with the circulation including blood clot in the vein in the liver (portal vein thrombosis); deep vein thrombosis; low blood pressure (hypotension); increased blood pressure; blocking of a blood vessel or (peripheral embolism); reduced blood flow in the hands, ankles or feet (peripheral ischaemia); swelling and clotting in a vein, which may be extremely tender when touched (phlebitis or thrombophlebitis superficial); blood clot (thrombosis);
  - a rare disorder characterised by periods of burning pain, redness and warmth in the feet and hands (erythromelalgia).

**Uncommon: may affect up to 1 in 100 people (may show up in blood or urine tests)**

- a rare type of anaemia in which the red blood cells, white blood cells and platelets are all reduced in number (aplastic anaemia);
- raised white blood cell count (leukocytosis);
- excess platelet production (thrombocythaemia); increased platelet counts; abnormal count in the cells in the blood that prevents bleeding (platelet count abnormal);
- changes in some blood tests (increase in transaminase; blood lactate dehydrogenase increased);
- or cancer of white blood cells (multiple myeloma);
- protein in the urine.



## Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Nplate

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

### Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

This medicine may be removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C). It must be returned to the refrigerator for storage longer than 24 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Nplate contains

- The active substance is romiplostim.

Each vial of Nplate 250 micrograms powder for solution for injection contains a total of 375 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 250 micrograms of romiplostim can be delivered. After reconstitution, a deliverable volume of 0.5 ml solution contains 250 micrograms of romiplostim (500 micrograms/ml).

Each vial of Nplate 500 micrograms powder for solution for injection contains a total of 625 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 500 micrograms of romiplostim can be delivered. After reconstitution, a deliverable volume of 1 ml solution contains 500 micrograms of romiplostim (500 micrograms/ml).

- The other ingredients are mannitol (E421), sucrose, L-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.

### What Nplate looks like and contents of the pack

Nplate is a white powder for solution for injection supplied in a 5 ml glass vial.

Carton containing 1 or 4 vials of either 250 micrograms or 500 micrograms of romiplostim.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer:**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**Marketing Authorisation Holder:**

Amgen Europe B.V.  
Minervum 7061  
4817 ZK Breda  
The Netherlands

**Manufacturer:**

Amgen Technology Ireland (ADL)  
Pottery Road  
Dun Laoghaire  
Co Dublin  
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

**België/Belgique/Belgien**

s.a. Amgen n.v.  
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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

**The following information is intended for healthcare professionals only:**

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 250 micrograms 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 (see vial content table below).

or

- **Nplate 500 micrograms 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 (see vial content table below).

Vial Content:

<b>Nplate single-use vial</b>	<b>Total vial content of romiplostim</b>		<b>Volume of sterile water for injection</b>		<b>Deliverable product and volume</b>	<b>Final concentration</b>
250 µg	375 µg	+	0.72 ml	=	250 µg in 0.5 ml	500 µg/ml
500 µg	625 µg	+	1.2 ml	=	500 µg in 1 ml	500 µg/ml

Sodium chloride solutions or bacteriostatic water should not be used when reconstituting the medicine.

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 discoloration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discoloration are observed.

From a microbiological point of view, the medicine 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°C – 8°C), protected from light.

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

## Package leaflet: Information for the user

### Nplate 250 micrograms powder and solvent for solution for injection Nplate 500 micrograms powder and solvent for solution for injection Romiplostim

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Nplate is and what it is used for
2. What you need to know before you use Nplate
3. How to use Nplate
4. Possible side effects
5. How to store Nplate
6. Contents of the pack and other information
7. Instructions for preparing and giving an injection of Nplate

#### **1. What Nplate is and what it is used for**

Nplate's active ingredient is romiplostim, which is a protein used to treat low platelet counts in patients with immune (idiopathic) thrombocytopenic purpura (called ITP). ITP is a disease in which your body's immune system destroys its own platelets. Platelets are the cells in your blood that help seal cuts and form blood clots. Very low platelet counts can cause bruising and serious bleeding.

Nplate is used to treat adult patients (aged 18 years and over) who may or may not have had their spleen removed for chronic ITP and who have been previously treated with corticosteroids or immunoglobulins, where these treatments don't work.

Nplate works by stimulating the bone marrow (part of the bone which makes blood cells) to produce more platelets. This should help to prevent bruising and bleeding associated with ITP.

#### **2. What you need to know before you use Nplate**

##### **Do not use Nplate:**

- if you are allergic to romiplostim or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines that are produced by DNA technology using the micro-organism *Escherichia coli* (*E. coli*).

##### **Warnings and precautions**

- If you stop taking Nplate a low blood platelet count (thrombocytopenia) is likely to reoccur. If you stop taking Nplate your platelet count will have to be monitored, and your doctor will discuss appropriate precautions with you.
- If you are at risk of blood clots or if blood clots are common in your family. The risk of blood clotting may also be increased if you:
  - have liver problems;

- are elderly ( $\geq 65$  years);
- are bedridden;
- have cancer;
- are taking the contraceptive pill or hormone replacement therapy;
- have recently had surgery or suffered an injury;
- are obese (overweight);
- are a smoker.

Talk to your doctor, pharmacist or nurse before using Nplate.

If you have very high blood platelet counts this may increase the risk of blood clotting. Your doctor will adjust your dose of Nplate to ensure that your platelet count does not become too high.

#### 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” and has been observed in Nplate clinical trials. It is not known if this may progress to a more severe form called “fibrosis.” Signs of bone marrow changes may show up as abnormalities in your blood tests. Your doctor will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate.

#### Worsening of blood cancers

Your doctor may decide to take a bone marrow biopsy if they decide it is necessary to ensure that you have ITP, and not another condition such as Myelodysplastic Syndrome (MDS). If you have MDS and receive Nplate you may have an increase in your blast cell counts and your MDS condition may worsen to become an acute myeloid leukaemia, which is a type of cancer of the blood.

#### Loss of response to romiplostim

If you experience a loss of response or failure to maintain a platelet response with romiplostim treatment, your doctor will investigate the reasons why including whether you are experiencing increased bone marrow fibres (reticulin) or have developed antibodies which neutralise romiplostim’s activity.

#### **Children and adolescents**

Nplate is not recommended for use in children below age 18.

#### **Other medicines and Nplate**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are also taking medicines which prevent blood clots (anticoagulants or antiplatelet therapy) there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking corticosteroids, danazol, and/or azathioprine, which you may be receiving to treat your ITP, these may be reduced or stopped when given together with Nplate.

#### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Nplate is not recommended for use if you are pregnant unless indicated by your doctor.

It is not known whether romiplostim is present in human milk. Nplate is not recommended for use if you are breast-feeding. A decision on whether to discontinue breast-feeding or discontinue therapy with romiplostim should be made taking into account the benefit of breast-feeding to your child and the benefit of romiplostim therapy to you.

### **Driving and using machines**

You should speak with your doctor before driving or using machines, as some side effects (e.g., temporary bouts of dizziness) may impair your ability to do so safely.

### **3. How to use Nplate**

Nplate will be given under the direct supervision of your doctor, who will closely control the amount of Nplate given to you.

Nplate is administered once a week as an injection under the skin (subcutaneous).

Your initial dose is 1 microgram of Nplate per kilogram of your body weight once a week. Your doctor will tell you how much you must take. Nplate should be injected once per week in order to keep your platelet counts up. Your doctor will take regular blood samples to measure how your platelets are responding and may adjust your dose as necessary.

Once your platelet count is under control, your doctor will continue to regularly check your blood. Your dose may be adjusted further in order to maintain long-term control of your platelet count.

Always use Nplate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure of how to use Nplate.

### **Instructions for preparing and giving an injection of Nplate**

After suitable training, your doctor may also allow you to inject Nplate yourself. Please read the instructions at the end of this leaflet on how to inject Nplate, as discussed with your doctor. If your doctor has allowed you to self-inject, you should follow up with your doctor every month to have the doctor determine if Nplate is working for you or if another treatment needs to be considered.

After the first month of self-injecting Nplate, you will need to show that you can still prepare and inject Nplate correctly.

### **If you use more Nplate than you should**

Your doctor will ensure that you receive the right amount of Nplate. If you have been given more Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may rise to very high levels and this may increase the risk of blood clotting. Therefore if your doctor suspects that you have been given more Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

If your doctor has allowed you to self-inject and you use more Nplate than you should, then inform your doctor immediately.

### **If you use less Nplate than you should**

Your doctor will ensure that you receive the right amount of Nplate. If you have been given less Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may become low and this may increase the risk of bleeding. Therefore if your doctor suspects that you

have been given less Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

If your doctor has allowed you to self-inject and you use less Nplate than you should, then inform your doctor immediately.

### **If you forget to use Nplate**

If you have missed a dose of Nplate, your doctor will discuss with you when you should have your next dose.

If your doctor has allowed you to self-inject and you forget to give yourself an injection, you should inform your doctor immediately.

### **If you stop using Nplate**

If you stop using Nplate, your low blood platelet count (thrombocytopenia) is likely to reoccur. Your doctor will decide if you should stop using Nplate.

### **Injecting Nplate yourself**

Your doctor may decide that it is best for you to inject Nplate. Your doctor, nurse or pharmacist will show you how to inject yourself with Nplate. Do not try to inject yourself if you have not been trained. It is very important that you prepare Nplate properly and take the correct dose (see section 7. Instructions for preparing and giving an injection of Nplate, at the end of this leaflet.)

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

### **Very common: may affect more than 1 in 10 people**

- headache;
- allergic reaction;
- upper respiratory tract infection.

### **Common: may affect up to 1 in 10 people**

- bone marrow disorder, including increased bone marrow fibres (reticulín);
- trouble sleeping (insomnia);
- dizziness;
- tingling or numbness of the hands or feet (paraesthesia);
- migraine;
- redness of the skin (flushing);
- blood clot in a lung artery (pulmonary embolism);
- nausea;
- diarrhoea;
- abdominal pain;
- indigestion (dyspepsia);
- constipation;
- itching of the skin (pruritis);
- bleeding under the skin (ecchymosis);
- bruising (contusion);
- rash;
- joint pain (arthralgia);
- muscles pain or weakness (myalgia);
- pain in your hands and feet;



- muscle spasm;
- back pain;
- bone pain;
- tiredness (fatigue);
- injection site reactions;
- swelling in the hands and feet (oedema peripheral);
- flu like symptoms (influenza like illness);
- pain;
- weakness (asthenia);
- fever (pyrexia);
- chills;
- contusion;
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema);
- gastroenteritis;
- palpitations.

**Common: may affect up to 1 in 10 people (may show up in blood or urine tests)**

- low blood platelet count (thrombocytopenia) and low blood platelet count (thrombocytopenia) after stopping Nplate;
- higher than normal platelet counts (thrombocytosis);
- anaemia.

**Uncommon: may affect up to 1 in 100 people**

- bone marrow failure; disorder of the bone marrow that causes scarring (myelofibrosis); enlarged spleen (splenomegaly); bleeding of the vagina (vaginal haemorrhage), bleeding in the rectum (rectal haemorrhage); bleeding mouth (mouth haemorrhage); injection site bleeding (injection site haemorrhage);
- heart attack (myocardial infarction); increased heart rate;
- dizziness or a spinning sensation (vertigo);
- problems with the eyes including: bleeding in the eye (conjunctival haemorrhage); difficulty focussing or blurred vision (accommodation disorder, papilloedema or eye disorder); blindness; itchy eye (eye pruritus); increased tears (lacrimation increased); or visual disturbances;
- problems with the digestive system including: vomiting; bad breath (breath odour); difficulty swallowing (dysphagia); indigestion or heartburn (gastro-oesophageal reflux disease); blood in the stools (haematochezia); stomach discomfort; mouth ulcers or mouth blistering (stomatitis); discoloured teeth (tooth discolouration);
- weight decreased; weight increased; intolerance of alcohol; loss of appetite (anorexia or decreased appetite); dehydration;
- generally feeling unwell (malaise); chest pain; irritability; swelling of the face (face oedema); feeling hot; increased body temperature; feeling jittery;
- influenza; localised infection; inflammation of the passages in the nose and throat (nasopharyngitis);
- problems with the nose and throat including: cough; runny nose (rhinorrhoea); dry throat; shortness of breath or difficulty breathing (dyspnoea); nasal congestion; painful breathing (painful respiration)
- painful swollen joints caused by uric acid (food breakdown product) (gout);
- muscle tightness; muscular weakness; shoulder pain; muscle twitching;
- problems with your nervous system including involuntary muscle contractions (clonus); distorted sense of taste (dysgeusia); decrease in sense of taste (hypogeusia); decreased feeling of sensitivity, especially in the skin (hypoesthesia); alteration in the nerve functions in the arms and legs (neuropathy peripheral); blood clot in the transverse sinus (transverse sinus thrombosis);
- depression; abnormal dreams;

- hair loss (alopecia); sensitivity to light (photosensitivity reaction); acne; allergic reaction in the skin upon contact with allergen (dermatitis contact); skin manifestation with rash and blisters (eczema); dry skin; redness of the skin (erythema); severe flaking or peeling rash (exfoliative rash); abnormal hair growth; thickening and itching of the skin due to repeated scratching (prurigo); bleeding beneath the surface of the skin or bruising under the skin (purpura); bumpy skin rash (rash papular); itchy skin rash (rash pruritic); generalised itchy rash (urticaria); bump on the skin (skin nodule); abnormal smell to the skin (skin odour abnormal);
- problems with the circulation including blood clot in the vein in the liver (portal vein thrombosis); deep vein thrombosis; low blood pressure (hypotension); increased blood pressure; blocking of a blood vessel or (peripheral embolism); reduced blood flow in the hands, ankles or feet (peripheral ischaemia); swelling and clotting in a vein, which may be extremely tender when touched (phlebitis or thrombophlebitis superficial); blood clot (thrombosis).
- a rare disorder characterised by periods of burning pain, redness and warmth in the feet and hands (erythromelalgia).

**Uncommon: may affect up to 1 in 100 people (may show up in blood or urine tests)**

- a rare type of anaemia in which the red blood cells, white blood cells and platelets are all reduced in number (aplastic anaemia);
- raised white blood cell count (leukocytosis);
- excess platelet production (thrombocythaemia); increased platelet counts; abnormal count in the cells in the blood that prevents bleeding (platelet count abnormal);
- changes in some blood tests (increase in transaminase; blood lactate dehydrogenase increased);
- or cancer of white blood cells (multiple myeloma);
- protein in the urine.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Nplate**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label after EXP. The expiry date refers to the last day of that month.

**Store in a refrigerator (2°C – 8°C).**

Do not freeze.

Store in the original carton in order to protect from light.

This medicine may be removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C). It must be returned to the refrigerator for storage longer than 24 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Nplate contains

- The active substance is romiplostim.

Each vial of Nplate 250 micrograms powder for solution for injection contains a total of 375 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 250 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 0.5 ml solution contains 250 micrograms of romiplostim (500 micrograms/ml).

Each vial of Nplate 500 micrograms powder for solution for injection contains a total of 625 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 500 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 1 ml solution contains 500 micrograms of romiplostim (500 micrograms/ml).

- The other ingredients are:  
Powder: mannitol (E421), sucrose, L-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.  
Solvent: water for injections.

### What Nplate looks like and contents of the pack

Nplate is a white powder for solution for injection supplied in a 5 ml glass vial.

Nplate is supplied as a 1 pack or multipack comprising 4 packs. Each pack contains:

- 1 vial of 250 micrograms or 500 micrograms of romiplostim.
- 1 pre-filled syringe containing 0.72 or 1.2 ml of water for injections.
- 1 plunger rod for pre-filled syringe.
- 1 sterile vial adapter.
- 1 sterile 1 ml Luer lock syringe.
- 1 sterile safety needle.
- 4 alcohol swabs.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer:

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The Netherlands

### Marketing Authorisation Holder:

Amgen Europe B.V.  
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4817 ZK Breda  
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### Manufacturer:

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>

**7. Instructions for preparing and giving an injection of Nplate**

This section contains information on how to give yourself an injection of Nplate. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse or pharmacist. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance. It is very important the product is prepared correctly and the correct dose is taken.

This section is divided into the following subsections:

Before you begin

- Step 1. Set up materials for an injection
- Step 2. Prepare vial for use, attach vial adapter
- Step 3. Prepare sterile water syringe
- Step 4. Dissolving Nplate by injecting water into vial
- Step 5. Prepare new syringe for injection
- Step 6. Prepare injection needle
- Step 7. Choose and prepare an injection site
- Step 8. Injecting the Nplate liquid
- Step 9. Disposing of supplies

**Before you begin**

**Read all instructions for use thoroughly.** These instructions are for patients who are already trained by their healthcare professional, such as your doctor, nurse, or pharmacist, in self injection. If you have not been trained, please contact your healthcare professional.

The Nplate self injection kit must be kept in the original package until use in order to protect the Nplate vial from light. Keep the Nplate self injection kit refrigerated at 2°C to 8°C.

Once Nplate has been dissolved, inject immediately.

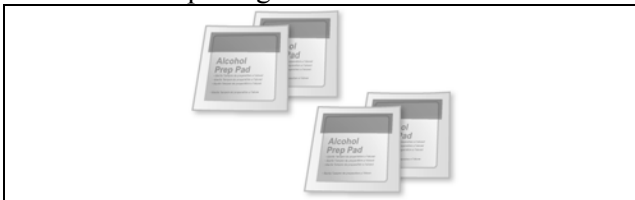
You may have excess Nplate left over after administering your prescribed dose. Do not re-use Nplate! Any excess dissolved Nplate must be thrown away immediately after completing the injection process. Left over Nplate in vial must NEVER be re-used for another injection.

## Step 1. Set up materials for an injection

### Do the following:

- Select a well lit, flat work surface, such as a table.
- Take the Nplate self injection kit out of the refrigerator. **Do not use if frozen.** If you have any questions about storage, contact your healthcare professional for further instructions. **Check the expiry date on the self injection kit. If the expiry date has passed, do not use.** Stop and contact your healthcare professional.
- **Note:** If your healthcare professional has instructed you that your Nplate dose requires more than one injection of Nplate<sub>2</sub>, you will need to use more than one self injection kit. Follow the steps as described in this leaflet and use as many self injection kits as necessary to complete your prescribed dose of Nplate.
- **Make sure you have the following items:**

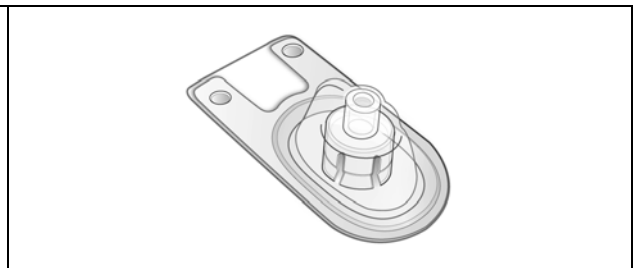
Alcohol swab package x4



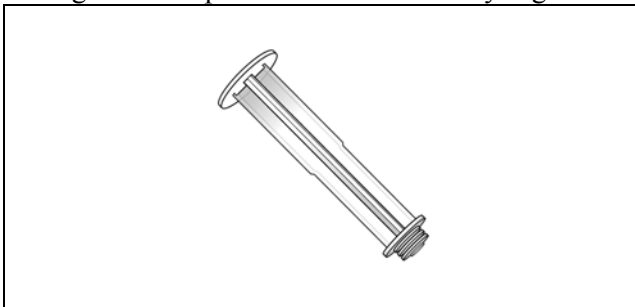
A vial of powder, either 250 micrograms OR 500 micrograms x1



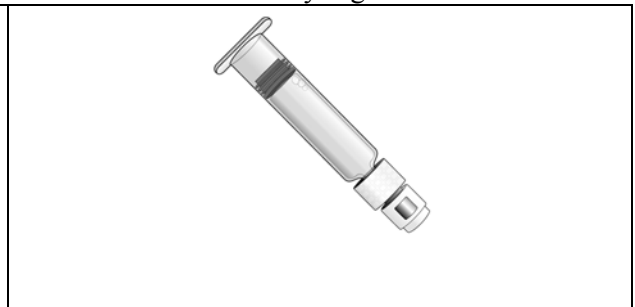
13 mm vial adapter x1



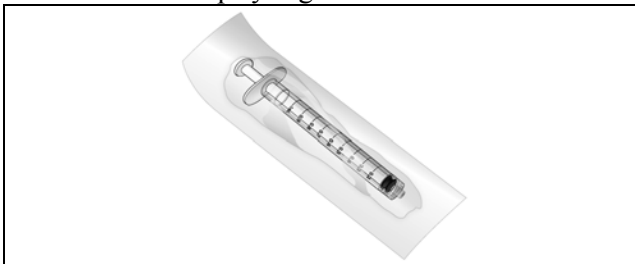
Plunger rod for pre-filled sterile water syringe x1



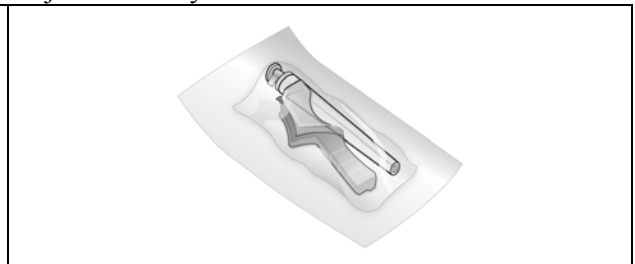
Pre-filled sterile water syringe x1



1 ml Luer-lock tip syringe x1



Injection safety needle x1



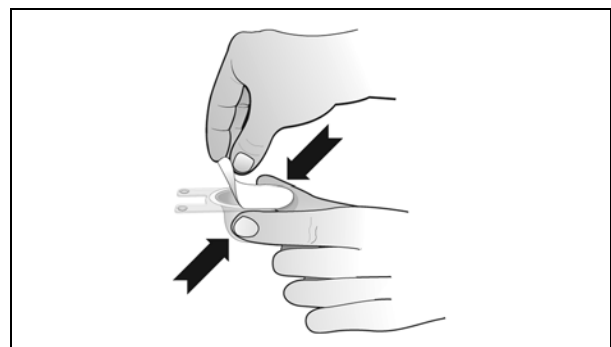
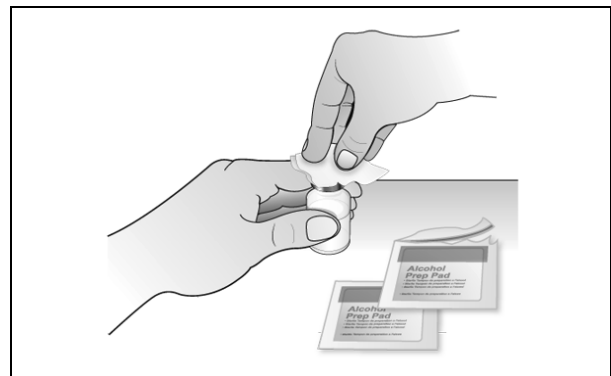
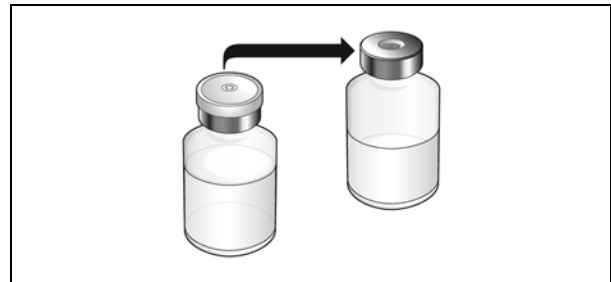
- **Do not** open items until directed in instructions.
- **Do not** use components that have evidence of tampering or damage.
- **Do not** re-use items.

**Step 2. Prepare vial for use, attach vial adapter**

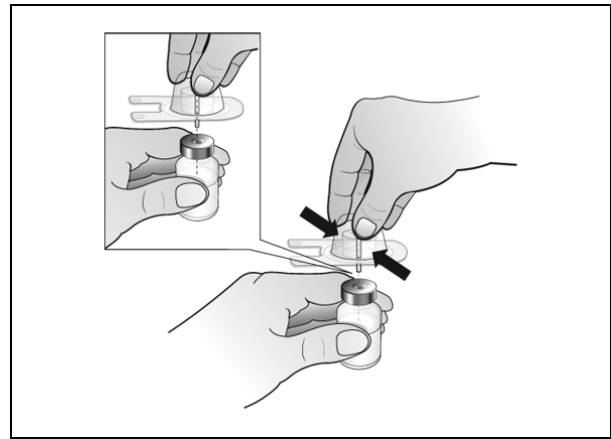
**Using:** 2 alcohol swab packages, 1 vial, and 1 vial adapter package.

**Do the following:**

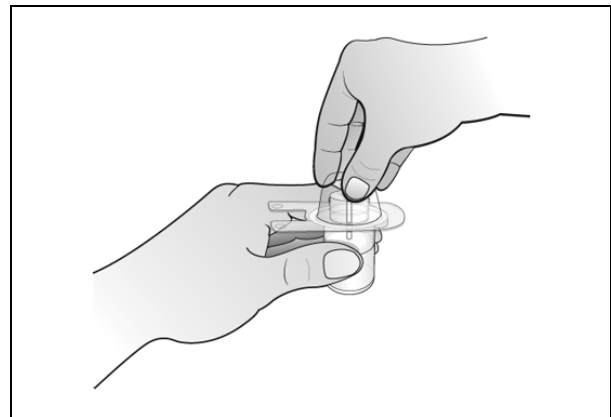
- **Wash your hands** with soap and warm water.
- **Clean the flat work surface with a new alcohol swab.**
- **Remove red (250 micrograms) or blue (500 micrograms) plastic cap from vial.**
- Using a new alcohol swab **clean vial stopper.**
- **Do not** touch vial stopper after cleaning it.
- **Peel off paper backing slowly from vial adapter while keeping vial adapter in the plastic package.**
- **Do not** touch vial stopper or spike of vial adapter.



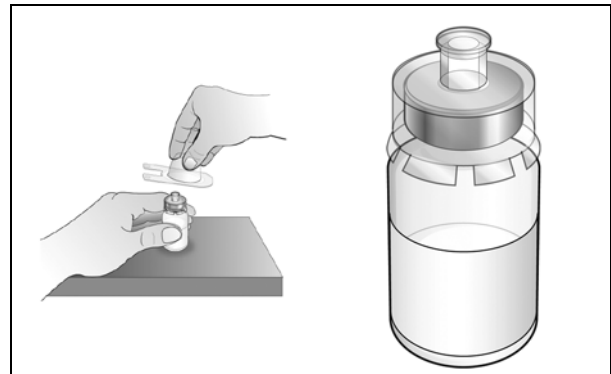
- Keeping the **vial on a table**, and keeping the vial adapter in the plastic packaging, **line up spike on the vial adapter to the centre of the stopper on the vial.**



- **Push the vial adapter down onto the vial until it is firmly in place** and you can't push down any more.



- **Lift off plastic vial adapter packaging, leaving vial adapter on vial.**
- **Do not touch the top of vial adapter.**



### Step 3. Prepare sterile water syringe

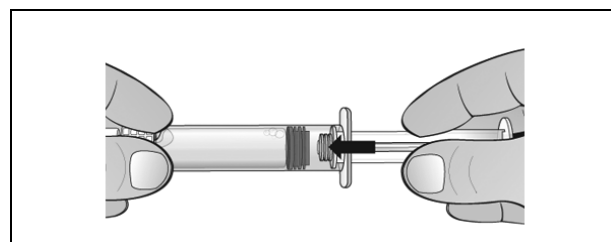
**Using:** Pre-filled sterile water syringe and plunger rod.

**Before you begin Step 3 please note the following:**

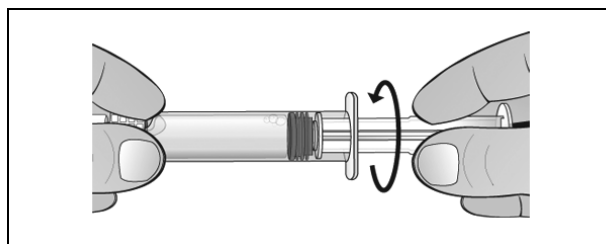
- The clear plastic plunger rod **MUST** always be attached first before breaking the white tip off of the pre-filled water syringe. Perform step 3a before step 3b.

**Do the following:**

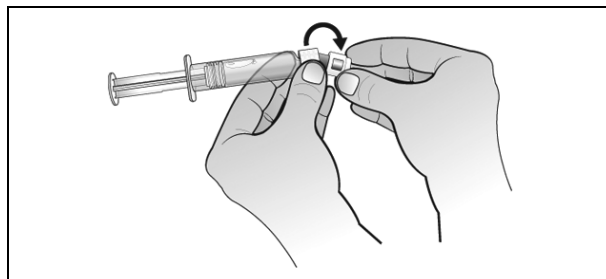
- **Step 3a: Attach clear plastic plunger rod to pre-filled sterile water syringe** by placing the threaded end of the plunger rod into the syringe and carefully twisting the rod clockwise onto the grey syringe plunger, until you feel a slight resistance. Do not over tighten.



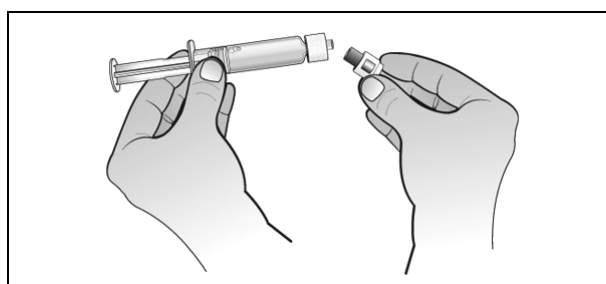




- **Step 3b: Holding the syringe with one hand, bend the tip of the white plastic cover downward with your other hand.** This will break the seal of the white plastic cover.



- Once the seal is broken, **pull the white plastic cover off.** You will see grey rubber in the cap.



#### **Step 4. Dissolving Nplate by injecting water into vial**

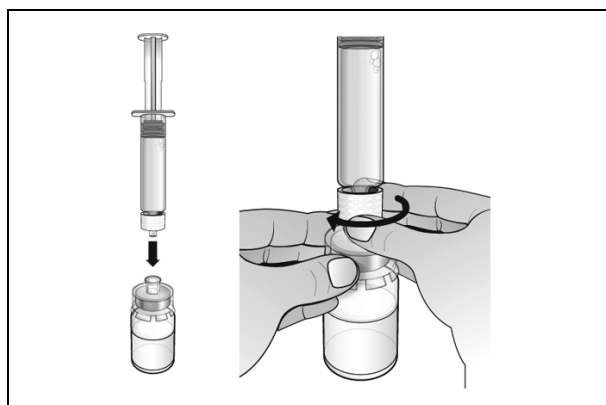
**Using:** Pre-filled sterile water syringe and vial with vial adapter attached.

**Before you begin Step 4 please note the following:**

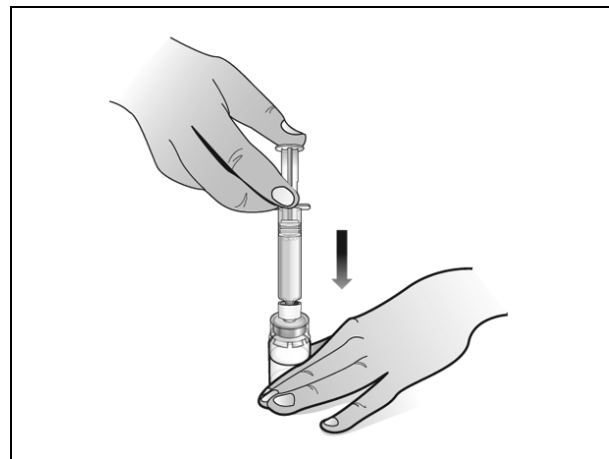
- **Do** dissolve slowly and carefully. This is a protein product and proteins can be easily damaged by improper mixing and excessive shaking.

**Do the following:**

- **Keeping the vial on the table, attach water-filled syringe to vial adapter** by holding the side of the vial adapter with one hand and twisting the syringe tip clockwise onto the adapter with the other hand until you feel a slight resistance.



- **Very slowly and gently push down on plunger rod to inject all water in the syringe into the vial.** Water must flow slowly onto powder.
- **Do not** force the water into the vial.
- Note: After injecting the water into the vial it is common for the plunger to move back up. You do not have to maintain pressure on the plunger for the rest of Step 4.

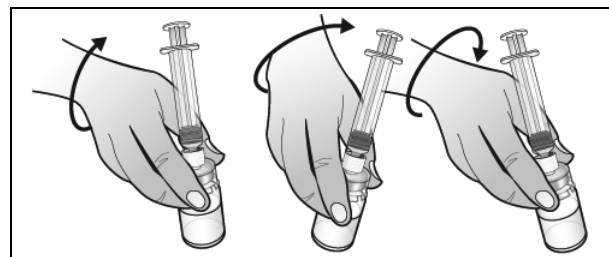


**Push slowly and gently**

**Before continuing:**

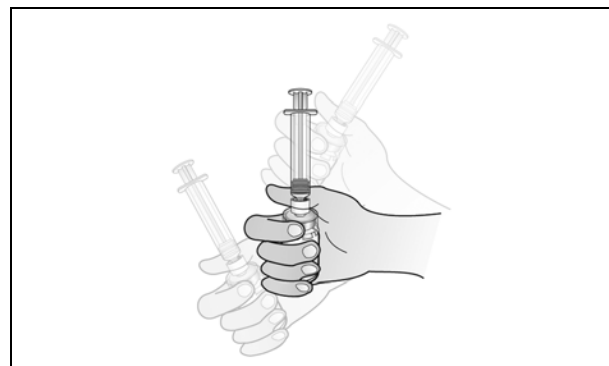
- **Do** ensure that all water is injected from the syringe into the vial before dissolving.

- **Holding the area where the vial and vial adapter connect between your fingers, gently swirl the vial by rotating your wrist until all of the powder has dissolved and the liquid in the vial is clear and colourless.**



**Correct**

- **Do** gently swirl the vial
- **Do not** shake the vial.
- **Do not** roll vial between palms
- **Note:** It may take up to 2 minutes for the powder to completely dissolve.

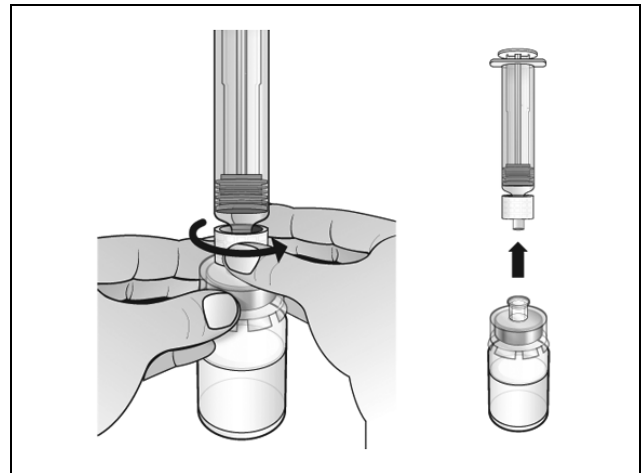


**Incorrect**

**Before continuing:**

- **Do** visually inspect the dissolved liquid for particles and/or discoloration. It must be clear and colourless and fully dissolved.
- Note: If there is **any colour or particles in the liquid**, contact your healthcare professional.
- **Do** make sure liquid is fully dissolved before removing syringe.

- **When Nplate is completely dissolved, remove the empty syringe by twisting it anti-clockwise off of the vial adapter.**



- **Discard the empty syringe** into sharps or hazard container. Keep the dissolved Nplate Vial. Immediately prepare new syringe for injection
- **Do not** delay injecting Nplate.

#### Step 5. Prepare new syringe for injection

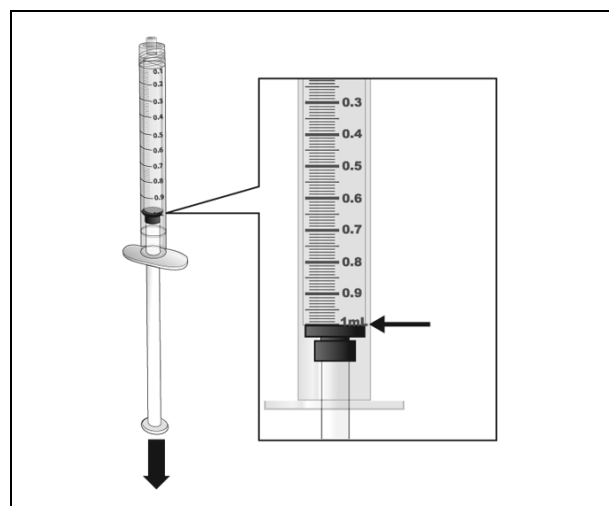
**Using:** A new 1 ml syringe package and the vial of dissolved, clear Nplate.

#### Before continuing:

- **Do** check your dose before starting this step. **Note:** The Nplate liquid is highly potent which is why accuracy and dose measurement are important.
- **Do** make sure that all air bubbles are removed before injection.

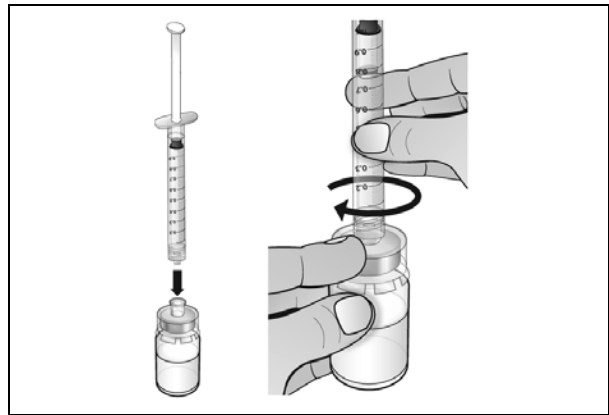
#### Do the following:

- **Remove 1 ml syringe from package.**
- **Draw air into syringe to 1 ml marking.**
- **Do not** pull plunger back to more than 1 ml.

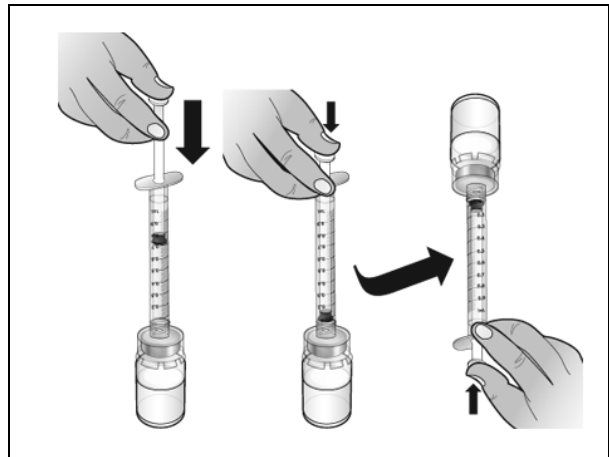


**Draw air into syringe to the 1 ml mark**

- **Attach 1 ml syringe to vial adapter** of the dissolved Nplate by twisting the syringe tip clockwise onto the vial adapter until you feel a slight resistance.

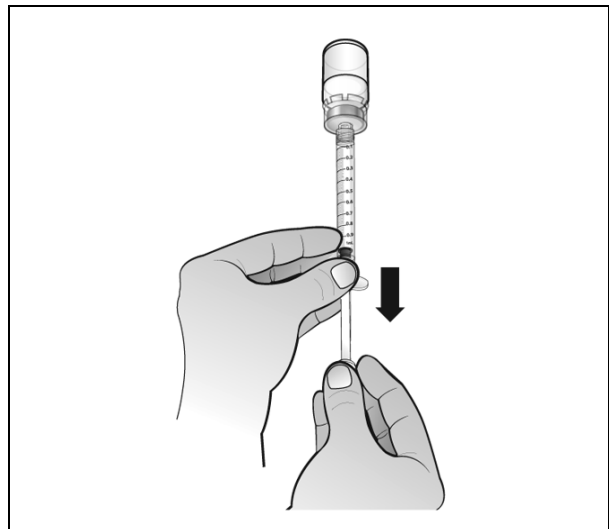


- Push air into vial.**
- Maintain pressure on plunger.**
- Turn vial assembly and syringe upside down**, so the vial is directly above the syringe.

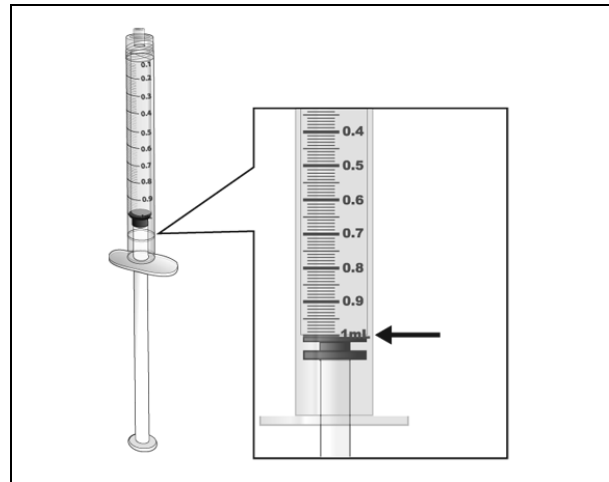


A. B. C.  
Flip

- **Withdraw the full amount of liquid into the syringe.**
  - The maximum deliverable volume for the 250 microgram vial is 0.5 ml and for the 500 microgram vial is 1 ml.
- **Do not pull the plunger out of the back of the syringe.**

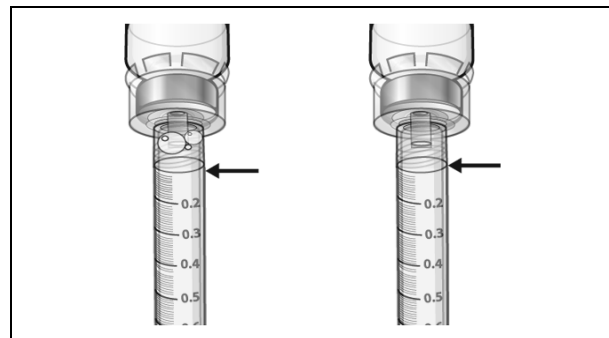


- **Do** ensure that the plunger remains in the syringe.



**Correct**

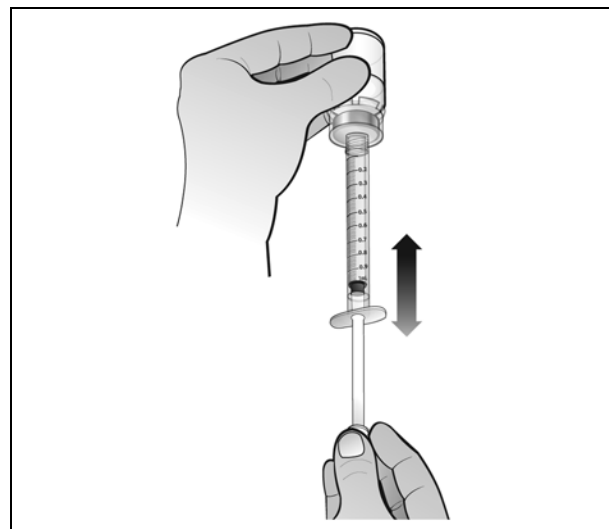
- **Check and remove all air bubbles in the syringe.**
  - Gently tap the syringe with your fingers to separate the bubbles from the liquid.
  - Slowly **push the plunger up** to force the air bubbles out of the syringe.



**Air bubbles:  
Incorrect**

**Correct**

- **Slowly push back on the plunger to leave only the amount prescribed by your healthcare professional.**
- **Make sure the top of the plunger head lines up with the syringe marking that matches your prescribed dose.** If necessary push liquid back into the vial to achieve the desired dose.



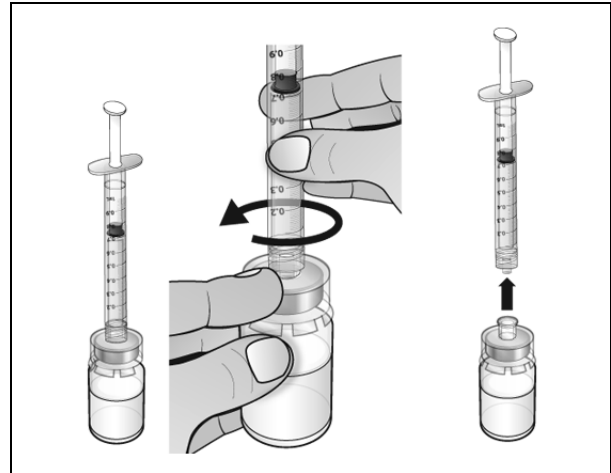
**Adjust the amount to your prescribed dose**

- **Do a final check to ensure the correct amount of liquid for your dose is in the syringe** and all air bubbles have been removed.

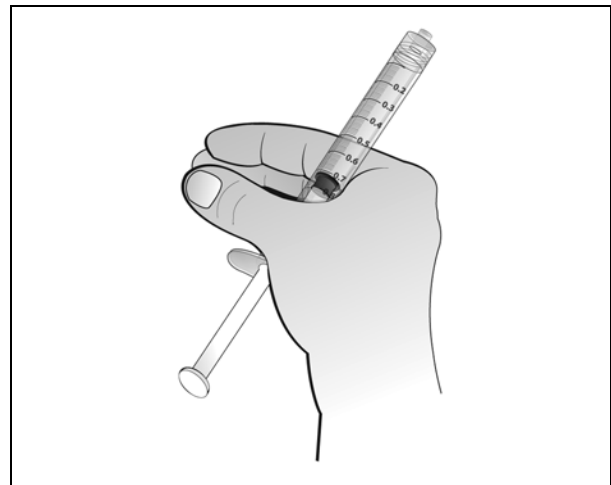
**Before continuing:**

- **Do** make sure the correct amount of liquid for your dose remains in the syringe.
- **Do** make sure all air bubbles are removed from the syringe.

- Once all air bubbles are removed and syringe is filled with your correct dose, **twist off syringe from vial adapter.**



- **Keep filled syringe in your hand and do not touch syringe tip.**
- **Do not** set filled syringe down after removing from vial.

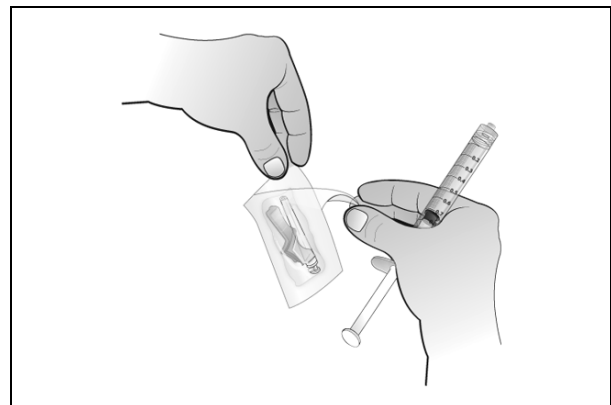


### Step 6. Prepare injection needle

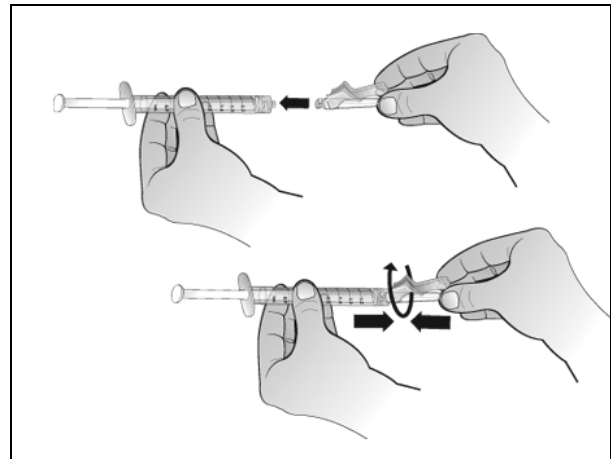
**Using:** Filled syringe with measured Nplate dose and safety needle.

#### Do the following:

- Holding the syringe in the palm of your hand with the tip facing up, **remove the safety needle from the package.**



- **Attach safety needle** to filled syringe. **Apply strong force while twisting to attach** the safety needle onto syringe. **Turn clockwise** to lock into Luer lock tip.
- The product is now ready for injection. **IMMEDIATELY** continue to step 7.

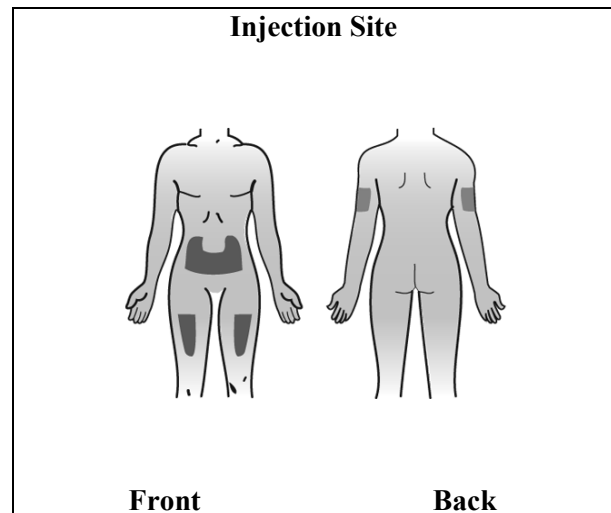


### Step 7. Choose and prepare an injection site

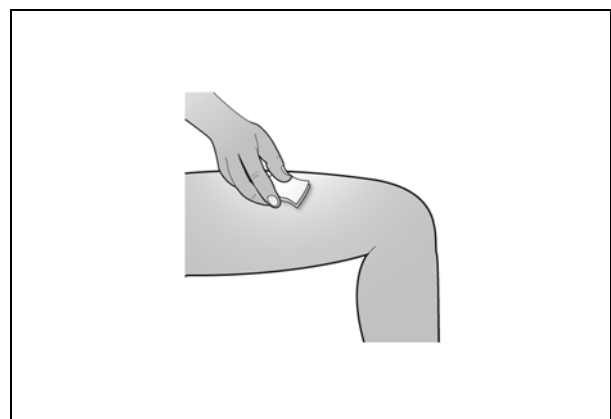
**Using:** New alcohol swab.

**Do the following:**

- **Select your injection site.** Three recommended injection sites for Nplate include:
  - Front of the middle thighs
  - Abdomen, except for the 5 centimetre area right around the navel
  - If someone else is giving you the injection, they can also use the outer area of the upper arms
  - **Do** rotate the site for each injection.



- **Do not inject into areas where the skin is tender, bruised and hard.**
- **Do not** inject into areas with scars or stretch marks.
- Wipe the site where Nplate is to be injected with an alcohol swab, using a circular motion.
- **Do not** touch this area again before giving the injection.

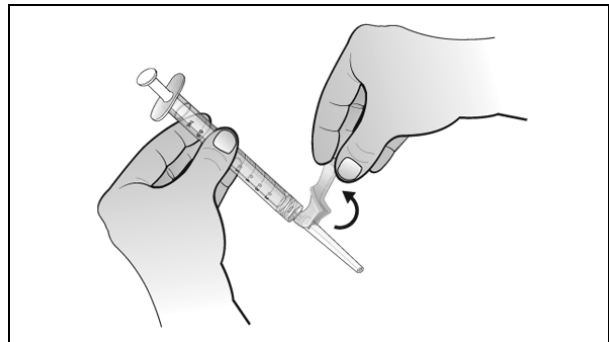


## Step 8. Injecting the Nplate liquid

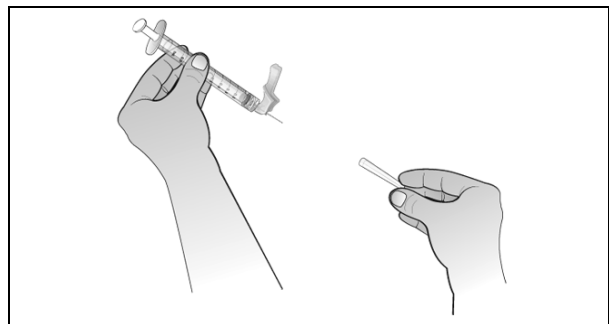
**Using:** Filled syringe and needle assembly.

**Do the following:**

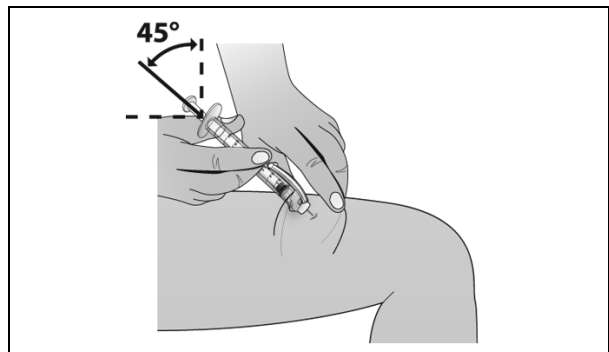
- **Pull back on the pink safety cover** (toward the syringe and away from the needle).



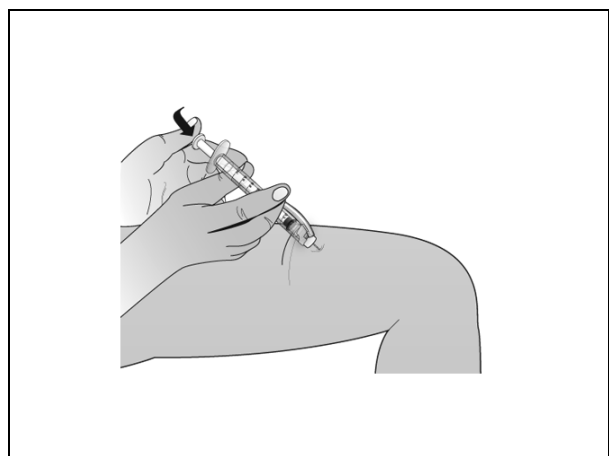
- **Remove clear needle shield** by holding syringe in one hand and carefully pulling shield straight off with the other hand.
- **Do not** remove the clear needle shield before injecting.



- With one hand, **gently pinch the cleaned area** of skin and hold it firmly. With the other hand, **hold the syringe (like a pencil) at a 45-degree angle** to the skin.
- With a short, sharp motion, **push the needle into the skin.**

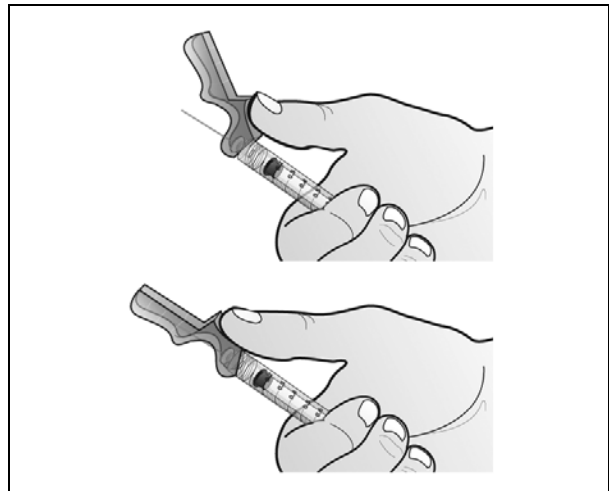


- Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.
- When the syringe is empty, pull the needle out of the skin, **being careful to keep it at the same angle as inserted.**
- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds.
- **Do not rub the injection site.** If needed, you may cover the injection site with a plaster.

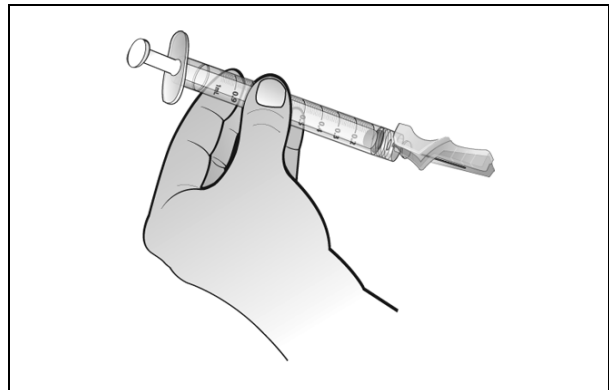




- **After injecting, use your thumb (or tip of your finger) to activate the pink safety cover** by pushing the cover forward using the same hand until you hear and/or feel it click and lock into place over the needle.



- **Visually confirm** that the needle tip is covered. Always cover the needle with the pink safety cover before disposal.



### Step 9. Disposing of supplies

#### Do the following:

- **Immediately discard syringe with covered needle** into a sharps container.
- **Immediately discard used Nplate vial** into an appropriate waste container.
- **Make sure all other materials are discarded into proper containers.**

The injection device and Nplate vial must **NEVER** be reused.

- **Do** dispose of the used needle and syringe in a puncture-resistant container.
- **Do** dispose of any left-over Nplate in proper waste container. **Left over Nplate in the vial must NEVER be re-used for another injection.**