ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nplate 125 micrograms powder for solution for injection
Nplate 250 micrograms powder for solution for injection
Nplate 500 micrograms powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nplate 125 micrograms powder for solution for injection

Each vial contains 125 mcg of romiplostim. After reconstitution, a deliverable volume of 0.25 mL solution contains 125 mcg of romiplostim (500 mcg/mL). An additional overfill is included in each vial to ensure that 125 mcg of romiplostim can be delivered.

Nplate 250 micrograms powder for solution for injection

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

Nplate 500 micrograms powder for solution for injection

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

Adults:

Nplate is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Paediatrics:

Nplate is indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in paediatric patients one year of age and older 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 mcg/kg based on actual body weight.

Dose calculation

The volume of romiplostim to administer is calculated based on body weight, dose required, and concentration of product.

Table 1. Guidelines for calculating individual patient dose and volume of romiplostim to administer

Individual patient dose (mcg)	Individual patient dose (mcg) = weight (kg) x dose in mcg/kg Actual body weight at initiation of treatment should always be used when calculating initial dose. • In adults, future dose adjustments are based on changes in platelet counts only. • In paediatric patients, future dose adjustments are based on changes in platelet counts and **changes in body weight**. Reassessment of body weight is recommended every 12 weeks.
If individual patient dose is ≥ 23 mcg	Reconstitute lyophilised product as described in section 6.6. The resulting concentration is 500 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg) / 500 mcg/mL (Round volume to the nearest hundredth mL)
If individual patient dose is < 23 mcg	Dilution is required to ensure accurate dosing. Reconstitute lyophilised product and then dilute the product as described in section 6.6. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg) / 125 mcg/mL (Round volume to the nearest hundredth mL)
Example	10 kg patient is initiated at 1 mcg/kg of romiplostim. Individual patient dose (mcg) = 10 kg x 1 mcg/kg = 10 mcg Because the dose is < 23 mcg, dilution is required to ensure accurate dosing. Reconstitute lyophilised product and then dilute the product as described in section 6.6. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = 10 mcg / 125 mcg/mL = 0.08 mL

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 mcg/kg until the patient achieves a platelet count ≥ 50 x 10^9/L. Platelet counts should be assessed weekly until a stable platelet count (≥ 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed monthly thereafter and appropriate dose adjustments made as per the dose adjustment table (table 2) in order to maintain platelet counts within the recommended range. See table 2 below for dose adjustment and monitoring. A maximum once weekly dose of 10 mcg/kg should not be exceeded.

Table 2. Dose adjustment guidance based on platelet count

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

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

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 mcg/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 under the age of one year has not been established.

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. If the calculated individual patient dose is less than 23 mcg, dilution with preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection is required to ensure accurate dosing (see section 6.6). 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.

Self-administration of Nplate is not allowed for paediatric patients.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Thrombotic/thromboembolic events including deep vein thrombosis, pulmonary embolism, and myocardial infarction have been observed with the use of romiplostim in the ITP population. These events have occurred regardless of platelet count (see section 4.8). 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. It is recommended to monitor patients for signs and symptoms of thrombotic/thromboembolic events and treat promptly as per institutional guidance and standard medical practice.

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. In some paediatric patients, accurate dosing relies on an additional dilution step after reconstitution which may increase the risk for medication errors (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 ITP (see section 4.1) 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 for those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

In adult 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 randomised 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 parametres 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 parametres 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 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.

MedDRA system organ class	**Very common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infection Rhinitis***	Gastroenteritis Pharyngitis*** Conjunctivitis*** Ear infection*** Sinusitis***/**** Bronchitis****	Influenza Localised infection Nasopharyngitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Multiple myeloma Myelofibrosis

MedDRA system organ class	Very common	Common	Uncommon
Blood and lymphatic system disorders		Bone marrow disorder* Thrombocytopenia* Anaemia	Aplastic anaemia Bone marrow failure Leucocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal
Immune system disorders	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	Oropharyngeal pain***	Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration

MedDRA system organ class	Very common	Common	Uncommon
Gastrointestinal disorders	Upper abdominal pain***	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 Peripheral swelling***	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
*** Additional adverse reactions observed in paediatric studies
**** Additional adverse reactions observed in adult patients with ITP duration up to 12 months

Adult population with ITP duration up to 12 months

The safety profile of romiplostim was similar across adult patients, regardless of ITP duration. Specifically in the integrated analysis of ITP ≤ 12 months duration (n = 311), 277 adult patients with ITP ≤ 12 months duration and who received at least one dose of romiplostim from among those patients in 9 ITP studies were included (see also section 5.1). In this integrated analysis, the following adverse reactions (at least 5% incidence and at least 5% more frequent with Nplate compared with placebo or standard of care) occurred in romiplostim patients with ITP duration up to 12 months, but were not observed in those adult patients with ITP duration > 12 months: bronchitis, sinusitis (reported commonly (≥ 1/100 to < 1/10)).

Paediatric population

In the paediatric studies, 282 paediatric ITP subjects were treated with romiplostim in 2 controlled and 3 uncontrolled clinical trials. The median duration of exposure was 65.4 weeks. The overall safety profile was similar to that seen in adults.

The paediatric adverse reactions are derived from each of the paediatric ITP randomised safety set (2 controlled clinical trials) and paediatric ITP safety set (2 controlled and 3 uncontrolled clinical trials) where the subject incidence was at least 5% higher in the romiplostim arm compared to placebo and at least a 5% subject incidence in romiplostim-treated subjects.

The most common adverse reactions in paediatric ITP patients 1 year and older were upper respiratory tract infection, rhinitis, cough, oropharyngeal pain, upper abdominal pain, diarrhoea, rash, pyrexia, contusion (reported very commonly (≥ 1/10)), and pharyngitis, conjunctivitis, ear infection, gastroenteritis, sinusitis, purpura, urticaria and peripheral swelling (reported commonly (≥ 1/100 to < 1/10)).

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in paediatric studies compared to those seen in adult studies.

Some of the adverse reactions seen in adults were reported more frequently in paediatric subjects such as cough, diarrhoea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in paediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in paediatric subjects.

Description of selected adverse reactions

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

Bleeding events

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

In the two adult 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)).

In the Phase 3 paediatric study, the mean (SD) number of composite bleeding episodes (see section 5.1) was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm.

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.

Thrombocytosis in paediatric subjects occurred uncommonly (≥ 1/1 000 to < 1/100), with a subject incidence of 1 (0.4%). Subject incidence was 1 (0.4%) for either grade ≥ 3 or serious thrombocytosis.

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 randomised placebo-controlled trial in MDS adult 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 adult 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).

In a paediatric clinical trial (see section 5.1), of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin at year 1 after exposure to romiplostim (cohort 1) and 17 out of 36 subjects (47.2%) developed increased reticulin at year 2 after exposure to romiplostim (cohort 2). However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Clinical trials in adult ITP patients examined antibodies to romiplostim and TPO. While 5.7% (60/1,046) and 3.2% (33/1 046) of the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 4 subjects were positive for neutralising antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. Of the 4 subjects, 2 subjects tested negative for neutralising antibodies to romiplostim at the subject's last timepoint (transient positive) and 2 subjects remained positive at the subject's last timepoint (persistent antibodies). The incidence of pre-existing antibodies to romiplostim and TPO was 3.3% (35/1 046) and 3.0% (31/1 046), respectively.

In paediatric studies, the incidence of binding antibodies to romiplostim at any time was 9.6% (27/282). Of the 27 subjects, 2 subjects had pre-existing binding non-neutralising romiplostim antibodies at baseline. Additionally, 2.8% (8/282) developed neutralising antibodies to romiplostim. A total of 3.9% (11/282) subjects had binding antibodies to TPO at any time during romiplostim treatment. Of these 11 subjects, 2 subjects had pre-existing binding non-neutralising antibodies to TPO. One subject (0.35%) had a weakly positive postbaseline result for neutralising antibodies against TPO while on study (consistently negative for anti-romiplostim antibodies) with a negative result at baseline. The subject showed a transient antibody response for neutralising antibodies against TPO, with a negative result at the subject's last timepoint tested within the study period.

In the post-marketing registry study, 19 confirmed paediatric patients were included. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralising antibodies to romiplostim. There were no antibodies detected to TPO. A total of 184 confirmed adult patients were included in this study; for these patients, the incidence of binding antibody post treatment was 3.8% (7/184) to romiplostim, of which 0.5% (1/184) was positive for neutralising antibodies to romiplostim. A total of 2.2% (4/184) adult patients developed binding, non-neutralising antibody against TPO.

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 1 000 mcg/kg or in monkeys after repeated administration of romiplostim at 500 mcg/kg (100 or 50 times the maximum clinical dose of 10 mcg/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: Antihaemorrhagics, other systemic haemostatics, 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 mcg/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 weeks period and the response was variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 mcg/kg of romiplostim were within the range of 50 to 450 $\times 10^9$/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 (20030212) evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior therapies. Patients had been diagnosed with ITP for a median of 2.1 years (range 0.1 to 31.6) at the time of study entry. Patients had received 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 10^9/L at study entry.

Study S2 (20030105) evaluated patients who were splenectomised and continued to have thrombocytopenia. Patients had been diagnosed with ITP for a median of 8 years (range 0.6 to 44.8) at the time of study entry. In addition to a splenectomy, patients had received 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 x 10^9/L at study entry.

Both studies were similarly designed. Patients (≥ 18 years) were randomised in a 2:1 ratio to receive a starting dose of romiplostim 1 mcg/kg or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain (50 to 200 x 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 mcg/kg and for non-splenectomised patients was 2 mcg/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 ≥ 50 x 10^9/L in between 50% to 70% of patients during the 6 months treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able to 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)
No. (%) patients with durable platelet response[a]	25 (61%)	1 (5%)	16 (38%)	0 (0%)	41 (50%)	1 (2%)
(95% CI)	(45%, 76%)	(0%, 24%)	(24%, 54%)	(0%, 16%)	(38%, 61%)	(0%, 13%)
p-value	< 0.0001		0.0013		< 0.0001	
No. (%) patients with overall platelet response[b]	36 (88%)	3 (14%)	33 (79%)	0 (0%)	69 (83%)	3 (7%)
(95% CI)	(74%, 96%)	(3%, 36%)	(63%, 90%)	(0%, 16%)	(73%, 91%)	(2%, 20%)
p-value	< 0.0001		< 0.0001		< 0.0001	
Mean no. weeks with platelet response[c]	15	1	12	0	14	1
(SD)	3.5	7.5	7.9	0.5	7.8	2.5
p-value	< 0.0001		< 0.0001		< 0.0001	
No. (%) patients requiring rescue therapies[d]	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	
No. (%) patients with durable platelet response with stable dose[e]	21 (51%)	0 (0%)	13 (31%)	0 (0%)	34 (41%)	0 (0%)
(95% CI)	(35%, 67%)	(0%, 16%)	(18%, 47%)	(0%, 16%)	(30%, 52%)	(0%, 8%)
p-value	0.0001		0.0046		< 0.0001	

[a] Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for study weeks 18-25 in the absence of rescue therapies any time during the treatment period.

[b] Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during study weeks 2-25 but without durable platelet response. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.

[c] Number of weeks with platelet response is defined as number of weeks with platelet counts ≥ 50 x 10^9/L during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.

[d] 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.
[e] Stable dose defined as dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment.

Results of studies in adult patients with newly diagnosed and persistent ITP

Study S3 (20080435) was a single arm, open label study in adult patients who had an insufficient response (platelet count ≤ 30 x 10^9/L) to first line therapy. The study enrolled 75 patients of whom the median age was 39 years (range 19 to 85) and 59% were female.

The median time from ITP diagnosis to study enrolment was 2.2 months (range 0.1 to 6.6). Sixty percent of patients (n = 45) had ITP duration < 3 months and 40% (n = 30) had ITP duration ≥ 3 months. The median platelet count at screening was 20 x 10^9/L. Prior ITP treatments included corticosteroids, immunoglobulins and anti D immunoglobulins. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, anti D immunoglobulin, dapsone, danazol, and azathioprine) were permitted.

Patients received single weekly SC injections of romiplostim over a 12-month treatment period, with individual dose adjustments to maintain platelet counts (50 x 10^9/L to 200 x 10^9/L). During the study, the median weekly romiplostim dose was 3 mcg/kg (25th 75th percentile: 2-4 mcg/kg).

Of the 75 patients enrolled in study 20080435, 70 (93%) had a platelet response ≥ 50 x 10^9/L during the 12-month treatment period. The mean number of months with platelet response during the 12-month treatment period was 9.2 (95% CI: 8.3, 10.1) months; the median was 11 (95% CI: 10, 11) months. The Kaplan Meier estimate of the median time to first platelet response was 2.1 weeks (95% CI: 1.1, 3.0). Twenty-four (32%) patients had sustained treatment-free remission as defined by maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months in the absence of romiplostim and any medication for ITP (concomitant or rescue); the median time to onset of maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months was 27 weeks (range 6 to 57).

In an integrated analysis of efficacy, 277 adult patients with ITP duration ≤ 12 months and who received at least one dose of romiplostim from among those patients in 9 ITP studies (inclusive of study S3) were included. Of the 277 romiplostim-treated patients, 140 patients had newly diagnosed ITP (ITP duration < 3 months) and 137 patients had persistent ITP (ITP duration ≥ 3 to ≤ 12 months). The percentage of patients achieving a durable platelet response, defined as at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment, was 50% (95% CI: 41.4% to 58.6%) for the 140 patients with newly diagnosed ITP and 55% (95% CI: 46.7% to 64.0%) for the 137 patients with persistent ITP. The median (Q1, Q3) percent time with a platelet response ≥ 50 x 10^9/L was 100.0% (70.3%, 100.0%) for patients with newly diagnosed ITP and 93.5% (72.2%, 100.0%) for patients with persistent ITP, respectively. Also, the percentage of patients requiring rescue medications was 47.4% for patients with newly diagnosed ITP and 44.9% for patients with persistent ITP.

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

Study S4 (20060131) was an open-label randomised 52 week trial in adult subjects who received romiplostim or medical standard of care (SOC) treatment. Patients had been diagnosed with ITP for a median of 2 years (range 0.01 to 44.2) at the time of study entry. This study evaluated non-splenectomised patients with ITP and platelet counts < 50 x 10^9/L. Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of 3 mcg/kg, and adjusted throughout the study within a range of 1-10 mcg/kg in order to maintain platelet counts between 50 and 200 x 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 mcg/kg (25th-75th percentile respectively; median 3 mcg/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 adult 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 adult ITP clinical programme an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (≥ grade 3) bleeding events occurred at platelet counts < 30 x 10^9/L. All bleeding events ≥ grade 2 occurred at platelet counts < 50 x 10^9/L. No statistically significant differences in the overall incidence of bleeding events were observed between romiplostim and placebo treated patients.

In the two adult 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 waived the obligation to submit data for children < 1 year.

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies. Study S5 (20080279) was a phase 3 study with 24 weeks of romiplostim treatment and study S6 (20060195) was a phase 1/2 study with 12 weeks of romiplostim treatment (up to 16 weeks for eligible responders who enter a 4-week pharmacokinetic assessment period).

Both studies enrolled paediatric subjects (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of 2 platelet counts ≤ 30 x 10^9/L with neither count > 35 x 10^9/L in both studies) with ITP, regardless of splenectomy status.

In study S5, 62 subjects were randomised in a 2:1 ratio to receive romiplostim (n = 42) or placebo (n = 20) and stratified into 1 of 3 age cohorts. The starting dose of romiplostim 1 mcg/kg and doses were adjusted to maintain (50 to 200 x 10^9/L) platelet counts. The most frequently used weekly dose was 3-10 mcg/kg and the maximum allowed dose on study was 10 mcg/kg. Patients received single subcutaneous weekly injections for 24 weeks. Of those 62 subjects, 48 subjects had ITP > 12 months of duration (32 subjects received romiplostim and 16 subjects received placebo).

The primary endpoint was the incidence of durable response, defined as achieving at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment. Overall, a significant greater proportion of subjects in the romiplostim arm achieved the primary endpoint compared with subjects in the placebo arm (p = 0.0018). A total of 22 subjects (52%) had durable platelet response in the romiplostim arm compared with 2 subjects (10%) in the placebo arm: ≥ 1 to < 6 years 38% versus 25%; ≥ 6 to < 12 years 56% versus 11%; ≥ 12 to < 18 years 56% versus 0.

In the subset of subjects with ITP > 12 months of duration, the incidence of durable response was also significantly greater in the romiplostim arm compared with the placebo arm (p = 0.0022). A total of 17 subjects (53.1%) had durable platelet response in the romiplostim arm compared with 1 subject (6.3%) in the placebo arm: ≥ 1 to < 6 years 28.6% versus 25%; ≥ 6 to < 12 years 63.6% versus 0%; ≥ 12 to < 18 years 57.1% versus 0%.

The composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event. The mean (SD) number of composite bleeding episodes was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.5 (0, 4.5) in the placebo arm. In the subset of subjects with ITP > 12 months of duration, the mean (SD) number of composite bleeding episodes was 2.1 (4.7) for the romiplostim arm and 4.2 (7.5) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.0 (0, 4) in the placebo arm. Because the statistical testing for the incidence of rescue medication use was not significant, no statistical test was done for the number of composite bleeding episodes endpoint.

In study S6, 22 subjects were randomised in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 mcg/kg every 2 weeks and the target platelet count was ≥ 50 x 10^9/L. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0008). Of those 22 subjects, 17 subjects had ITP > 12 months of duration (14 subjects received romiplostim and 3 subjects received placebo). Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0147).

Paediatric subjects who had completed a prior romiplostim study (including study S5) were allowed to enrol in study S7 (20090340), an open-label extension study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic paediatric subjects with ITP.

A total of 66 subjects were enrolled in this study, including 54 subjects (82%) who had completed study S5. Of these, 65 subjects (98.5%) received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg). Of the 66 subjects enrolled in the study, 63 subjects had ITP > 12 months of duration. All the 63 subjects received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 138.0 weeks (91.1 weeks, 186.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg).

Across the study, the overall subject incidence of platelet response (1 or more platelet count ≥ 50 x 10^9/L in the absence of rescue medication) was 93.8% (n = 61) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 34.0 months (24.0 months, 46.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

In the subset of subjects with ITP > 12 months of duration, the overall subject incidence of platelet response was 93.7% (n = 59) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 35.0 months (23.0 months, 47.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

A total of 31 subjects (47.7%) used concurrent ITP therapy during the study including 23 subjects (35.4%) who used rescue medication and 5 subjects (7.7%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 30.8% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

In the subset of subjects with ITP > 12 months of duration, 29 subjects (46.0%) used concurrent ITP therapy during the study including 21 subjects (33.3%) who used rescue medication and 5 subjects (7.9%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 31.7% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

The subject prevalence of rescue medication use showed a trend towards a reduction over the course of the study: from 24.6% (weeks 1 to 12) to < 13.0% (weeks 13 to 216), then 0% after week 216 until the end of the study. Similar reduction of the subject prevalence of rescue medication over the course of the study was seen in the subset of subjects with ITP > 12 months of duration: from 25.4% (weeks 1 to 12) to ≤ 13.1% (weeks 13 to 216), then 0% after week 216 until the end of the study.

Study S8 (20101221) was a phase 3, long-term, single-arm, open-label, multicentre study conducted in 203 paediatric patients with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies. Romiplostim was administered weekly by subcutaneous injection starting at a dose of 1 mcg/kg with weekly increments to a maximum dose of 10 mcg/kg to reach a target platelet count between 50 x 10^9/L and 200 x 10^9/L. The median age of the patients was 10 years (range 1 to 17 years) and the median duration of treatment were 155.9 (range, 8.0 to 163.0) weeks.

The mean (SD) and median percentage of time with a platelet response (platelet count ≥ 50 x 10^9/L) within the first 6 months of initiation of romiplostim without rescue medication use for the past 4 weeks was 50.57% (37.01) and 50.0%, respectively. Sixty (29.6%) subjects overall received rescue medications. Rescue medications (i.e., corticosteroids, platelet transfusions, IVIG, azathioprine, anti-D immunoglobulin, and danazol) were permitted.

Study S8 also evaluated bone marrows for reticulin and collagen formation as well as for abnormalities in paediatric patients with ITP receiving romiplostim treatment. The modified Bauermeister grading scale was used for reticulin and collagen assessments, whereas cytogenetics and fluorescence *in situ* hybridization (FISH) were used to evidence bone marrow abnormalities. Based on cohort assignment at the time of study enrolment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1) or year 2 (cohort 2) in comparison to the baseline bone marrow at the start of the study. From the total of 79 patients enrolled in the 2 cohorts, 27 of 30 (90%) patients in cohort 1 and 36 of 49 (73.5%) patients in cohort 2 had evaluable on-study bone marrow biopsies. Increased reticulin fibre formation was reported for 18.5% (5 of 27) of patients in cohort 1 and 47.2% (17 of 36) of patients in cohort 2. No patients in either cohort developed collagen fibrosis or a bone marrow abnormality that was inconsistent with an underlying diagnosis of ITP.

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 mcg/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 mcg/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 mcg/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.

Paediatric population

Pharmacokinetic data of romiplostim were collected from two studies in 21 paediatric subjects with ITP. In study S6 (20060195), romiplostim concentrations were available from 17 subjects at doses ranging from 1 to 10 mcg/kg. In Study S7 (20090340), intensive romiplostim concentrations were available from 4 subjects (2 at 7 mcg/kg and 2 at 9 mcg/kg). Serum concentrations of romiplostim in paediatrics with ITP were within the range observed in adult ITP subjects receiving the same dose range of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in paediatric subjects with ITP and are not reliable and predictive. However, the data are insufficient to draw any meaningful conclusion relating to the impact of dose and age on the pharmacokinetics of romiplostim.

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.

After dilution: Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C when the diluted product was held in a disposable syringe, or 4 hours in a refrigerator (2°C – 8°C) when the diluted product was held in the original vial.

From a microbiological point of view, the diluted 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 4 hours at 25°C in disposable syringes, or 4 hours in a refrigerator (2°C – 8°C) in the original vials, 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 removed from the refrigerator for a period of 30 days at room temperature (up to 25°C) when stored in the original carton.

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

6.5 Nature and contents of container

Single-dose vial (type 1 clear glass) with a stopper (chlorobutyl rubber), seal (aluminium) and a flip-off cap (polypropylene). The 125 mcg vial cap is beige, the 250 mcg vial cap is red and the 500 mcg vial cap is blue.

Carton containing 1 or 4 vials of romiplostim.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution

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 125 micrograms powder for solution for injection

Nplate 125 micrograms powder for solution for injection should be reconstituted with 0.44 mL sterile water for injections, yielding a deliverable volume of 0.25 mL. An additional overfill is included in each vial to ensure that 125 mcg of romiplostim can be delivered (see vial content table below).

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 mcg 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 mcg 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**
125 mcg	230 mcg	+	0.44 mL	=	125 mcg in 0.25 mL	500 mcg/mL
250 mcg	375 mcg	+	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL
500 mcg	625 mcg	+	1.20 mL	=	500 mcg in 1.00 mL	500 mcg/mL

Sterile water for injections only should be used when reconstituting the medicinal product. Sodium chloride solutions or bacteriostatic water should not be used when reconstituting the medicinal product.

Water for injections should be injected into the vial. The vial contents may be swirled gently and inverted during dissolution. The vial should not be shaken or vigorously agitated. Generally, dissolution of Nplate takes less than 2 minutes. Visually inspect the solution for particulate matter and discolouration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discolouration are observed.

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.

Dilution (required when the calculated individual patient dose is less than 23 mcg)

Initial reconstitution of romiplostim with designated volumes of sterile water for injections results in a concentration of 500 mcg/mL in all vial sizes. If the calculated individual patient dose is less than 23 mcg (see section 4.2), an additional dilution step to 125 mcg/mL with **preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection** is required to ensure accurate volume (see table below).

Dilution Guidelines:

Nplate single-use vial	Add this volume of preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection to the **reconstituted vial**	Concentration after dilution
125 mcg	1.38 mL	125 mcg/mL
250 mcg	2.25 mL	125 mcg/mL
500 mcg	3.75 mL	125 mcg/mL

Preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection only must be used for dilution. Dextrose (5%) in water or sterile water for injection should not be used for the dilution. No other diluents have been tested.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/497/009
EU/1/08/497/010
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 mcg of romiplostim. After reconstitution, a deliverable volume of 0.5 mL solution contains 250 mcg of romiplostim (500 mcg/mL). An additional overfill is included in each vial to ensure that 250 mcg of romiplostim can be delivered.

Nplate 500 micrograms powder and solvent for solution for injection

Each vial contains 500 mcg of romiplostim. After reconstitution, a deliverable volume of 1 mL solution contains 500 mcg of romiplostim (500 mcg/mL). An additional overfill is included in each vial to ensure that 500 mcg 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 the treatment of primary immune thrombocytopenia (ITP) in adult 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 mcg/kg based on actual body weight.

Dose calculation

Initial or subsequent once weekly dose:	Weight* in kg x Dose in mcg/kg = Individual patient dose in mcg
Volume to administer:	Dose in mcg x $\frac{1 \text{ mL}}{500 \text{ mcg}}$ = Amount to inject in mL
Example:	75 kg patient is initiated at 1 mcg/kg of romiplostim. The individual patient dose = 75 kg x 1 mcg/kg = 75 mcg The corresponding amount of Nplate solution to inject = 75 mcg x $\frac{1 \text{ mL}}{500 \text{ mcg}}$ = 0.15 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 mcg/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 mcg/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 mcg/kg should not be exceeded.

Adjust the dose as follows:

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

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

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 mcg/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 250/500 mcg powder and solvent for solution for injection, also used for self-administration in eligible adult patients, have not been established in patients aged under 18 years. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Self-administration of romiplostim is not allowed for paediatric patients. No data are available.

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

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 10^9/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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Thrombotic/thromboembolic events including deep vein thrombosis, pulmonary embolism, and myocardial infarction have been observed with the use of romiplostim in the ITP population. These events have occurred regardless of platelet count (see section 4.8). 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. It is recommended to monitor patients for signs and symptoms of thrombotic/thromboembolic events and treat promptly as per institutional guidance and standard medical practice.

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 ITP (see section 4.1) 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 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 randomised 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 parametres 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 parametres 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 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.

MedDRA system organ class	**Very common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infection Rhinitis***	Gastroenteritis Pharyngitis*** Conjunctivitis*** Ear infection*** Sinusitis***/**** Bronchitis****	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 Leucocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal
Immune system disorders	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

MedDRA system organ class	Very common	Common	Uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain***	Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration
Gastrointestinal disorders	Upper abdominal pain***	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 Peripheral swelling***	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
*** Additional adverse reactions observed in paediatric studies
**** Additional adverse reactions observed in adult patients with ITP duration up to 12 months

Adult population with ITP duration up to 12 months

The safety profile of romiplostim was similar across adult patients, regardless of ITP duration. Specifically in the integrated analysis of ITP ≤ 12 months duration (n = 311), 277 adult patients with ITP ≤ 12 months duration and who received at least one dose of romiplostim from among those patients in 9 ITP studies were included (see also section 5.1). In this integrated analysis, the following adverse reactions (at least 5% incidence and at least 5% more frequent with Nplate compared with placebo or standard of care) occurred in romiplostim patients with ITP duration up to 12 months, but were not observed in those adult patients with ITP duration > 12 months: bronchitis, sinusitis (reported commonly (≥ 1/100 to < 1/10)).

Paediatric population

In the paediatric studies, 282 paediatric ITP subjects were treated with romiplostim in 2 controlled and 3 uncontrolled clinical trials. The median duration of exposure was 65.4 weeks. The overall safety profile was similar to that seen in adults.

The paediatric adverse reactions are derived from each of the paediatric ITP randomised safety set (2 controlled clinical trials) and paediatric ITP safety set (2 controlled and 3 uncontrolled clinical trials) where the subject incidence was at least 5% higher in the romiplostim arm compared to placebo and at least a 5% subject incidence in romiplostim-treated subjects.

The most common adverse reactions in paediatric ITP patients 1 year and older were upper respiratory tract infection, rhinitis, cough, oropharyngeal pain, upper abdominal pain, diarrhoea, rash, pyrexia, contusion (reported very commonly (≥ 1/10)), and pharyngitis, conjunctivitis, ear infection, gastroenteritis, sinusitis, purpura, urticaria and peripheral swelling (reported commonly (≥ 1/100 to < 1/10)).

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in paediatric studies compared to those seen in adult studies.

Some of the adverse reactions seen in adults were reported more frequently in paediatric subjects such as cough, diarrhoea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in paediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in paediatric subjects.

Description of selected adverse reactions

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

Bleeding events

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

In the two adult 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)).

In the Phase 3 paediatric study, the mean (SD) number of composite bleeding episodes (see section 5.1) was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm.

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.

Thrombocytosis in paediatric subjects occurred uncommonly (≥ 1/1 000 to < 1/100), with a subject incidence of 1 (0.4%). Subject incidence was 1 (0.4%) for either grade ≥ 3 or serious thrombocytosis.

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 randomised 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).

In a paediatric clinical trial (see section 5.1), of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin at year 1 after exposure to romiplostim (cohort 1) and 17 out of 36 subjects (47.2%) developed increased reticulin at year 2 after exposure to romiplostim (cohort 2). However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Clinical trials in adult ITP patients examined antibodies to romiplostim and TPO. While 5.7% (60/1,046) and 3.2% (33/1 046) of

the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 4 subjects were positive for neutralising antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. Of the 4 subjects, 2 subjects tested negative for neutralising antibodies to romiplostim at the subject's last timepoint (transient positive) and 2 subjects remained positive at the subject's last timepoint (persistent antibodies). The incidence of pre-existing antibodies to romiplostim and TPO was 3.3% (35/1 046) and 3.0% (31/1 046), respectively.

In paediatric studies, the incidence of binding antibodies to romiplostim at any time was 9.6% (27/282). Of the 27 subjects, 2 subjects had pre-existing binding non-neutralising romiplostim antibodies at baseline. Additionally, 2.8% (8/282) developed neutralising antibodies to romiplostim. A total of 3.9% (11/282) subjects had binding antibodies to TPO at any time during romiplostim treatment. Of these 11 subjects, 2 subjects had pre-existing binding non-neutralising antibodies to TPO. One subject (0.35%) had a weakly positive postbaseline result for neutralising antibodies against TPO while on study (consistently negative for anti-romiplostim antibodies) with a negative result at baseline. The subject showed a transient antibody response for neutralising antibodies against TPO, with a negative result at the subject's last timepoint tested within the study period.

In the post-marketing registry study, 19 confirmed paediatric patients were included. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralising antibodies to romiplostim. There were no antibodies detected to TPO. A total of 184 confirmed adult patients were included in this study; for these patients, the incidence of binding antibody post treatment was 3.8% (7/184) to romiplostim, of which 0.5% (1/184) was positive for neutralising antibodies to romiplostim. A total of 2.2% (4/184) adult patients developed binding, non-neutralising antibody against TPO.

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 1 000 mcg/kg or in monkeys after repeated administration of romiplostim at 500 mcg/kg (100 or 50 times the maximum clinical dose of 10 mcg/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: Antihaemorrhagics, other systemic haemostatics, 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 mcg/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 weeks period and the response was variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 mcg/kg of romiplostim were within the range of 50 to 450 x 10^9/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 (20030212) evaluated patients who were non-splenectomised and had an inadequate response or were intolerant to prior therapies. Patients had been diagnosed with ITP for a median of 2.1 years (range 0.1 to 31.6) at the time of study entry. Patients had received 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 10^9/L at study entry.

Study S2 (20030105) evaluated patients who were splenectomised and continued to have thrombocytopenia. Patients had been diagnosed with ITP for a median of 8 years (range 0.6 to 44.8) at the time of study entry. In addition to a splenectomy, patients had received 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 x 10^9/L at study entry.

Both studies were similarly designed. Patients (≥ 18 years) were randomised in a 2:1 ratio to receive a starting dose of romiplostim 1 mcg/kg or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain (50 to 200 x 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 mcg/kg and for non-splenectomised patients was 2 mcg/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 ≥ 50 x 10^9/L in between 50% to 70% of patients during the 6 months treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able to 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)
No. (%) patients with durable platelet response[a]	25 (61%)	1 (5%)	16 (38%)	0 (0%)	41 (50%)	1 (2%)
(95% CI)	(45%, 76%)	(0%, 24%)	(24%, 54%)	(0%, 16%)	(38%, 61%)	(0%, 13%)
p-value	< 0.0001		0.0013		< 0.0001	
No. (%) patients with overall platelet response[b]	36 (88%)	3 (14%)	33 (79%)	0 (0%)	69 (83%)	3 (7%)
(95% CI)	(74%, 96%)	(3%, 36%)	(63%, 90%)	(0%, 16%)	(73%, 91%)	(2%, 20%)
p-value	< 0.0001		< 0.0001		< 0.0001	
Mean no. weeks with platelet response[c]	15	1	12	0	14	1
(SD)	3.5	7.5	7.9	0.5	7.8	2.5
p-value	< 0.0001		< 0.0001		< 0.0001	
No. (%) patients requiring rescue therapies[d]	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	
No. (%) patients with durable platelet response with stable dose[e]	21 (51%)	0 (0%)	13 (31%)	0 (0%)	34 (41%)	0 (0%)
(95% CI)	(35%, 67%)	(0%, 16%)	(18%, 47%)	(0%, 16%)	(30%, 52%)	(0%, 8%)
p-value	0.0001		0.0046		< 0.0001	

[a] Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for study weeks 18-25 in the absence of rescue therapies any time during the treatment period.

[b] Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during study weeks 2-25 but without durable platelet response. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.

[c] Number of weeks with platelet response is defined as number of weeks with platelet counts ≥ 50 x 10^9/L during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.

[d] 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.
[e] Stable dose defined as dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment.

Results of studies in adult patients with newly diagnosed and persistent ITP

Study S3 (20080435) was a single arm, open label study in adult patients who had an insufficient response (platelet count ≤ 30 x 10^9/L) to first line therapy. The study enrolled 75 patients of whom the median age was 39 years (range 19 to 85) and 59% were female.

The median time from ITP diagnosis to study enrolment was 2.2 months (range 0.1 to 6.6). Sixty percent of patients (n = 45) had ITP duration < 3 months and 40% (n = 30) had ITP duration ≥ 3 months. The median platelet count at screening was 20 x 10^9/L. Prior ITP treatments included corticosteroids, immunoglobulins and anti D immunoglobulins. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, anti D immunoglobulin, dapsone, danazol, and azathioprine) were permitted.

Patients received single weekly SC injections of romiplostim over a 12-month treatment period, with individual dose adjustments to maintain platelet counts (50 x 10^9/L to 200 x 10^9/L). During the study, the median weekly romiplostim dose was 3 mcg/kg (25th-75th percentile: 2-4 mcg/kg).

Of the 75 patients enrolled in study 20080435, 70 (93%) had a platelet response ≥ 50 x 10^9/L during the 12-month treatment period. The mean number of months with platelet response during the 12-month treatment period was 9.2 (95% CI: 8.3, 10.1) months; the median was 11 (95% CI: 10, 11) months. The Kaplan Meier estimate of the median time to first platelet response was 2.1 weeks (95% CI: 1.1, 3.0). Twenty-four (32%) patients had sustained treatment-free remission as defined by maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months in the absence of romiplostim and any medication for ITP (concomitant or rescue); the median time to onset of maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months was 27 weeks (range 6 to 57).

In an integrated analysis of efficacy, 277 adult patients with ITP duration ≤ 12 months and who received at least one dose of romiplostim from among those patients in 9 ITP studies (inclusive of study S3) were included. Of the 277 romiplostim-treated patients, 140 patients had newly diagnosed ITP (ITP duration < 3 months) and 137 patients had persistent ITP (ITP duration ≥ 3 to ≤ 12 months). The percentage of patients achieving a durable platelet response, defined as at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment, was 50% (95% CI: 41.4% to 58.6%) for the 140 patients with newly diagnosed ITP and 55% (95% CI: 46.7% to 64.0%) for the 137 patients with persistent ITP. The median (Q1, Q3) percent time with a platelet response ≥ 50 x 10^9/L was 100.0% (70.3%, 100.0%) for patients with newly diagnosed ITP and 93.5% (72.2%, 100.0%) for patients with persistent ITP, respectively. Also, the percentage of patients requiring rescue medications was 47.4% for patients with newly diagnosed ITP and 44.9% for patients with persistent ITP.

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

Study S4 (20060131) was an open-label randomised 52 week trial in subjects who received romiplostim or medical standard of care (SOC) treatment. Patients had been diagnosed with ITP for a median of 2 years (range 0.01 to 44.2) at the time of study entry. This study evaluated non-splenectomised patients with ITP and platelet counts < 50 x 10^9/L. Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of 3 mcg/kg, and adjusted throughout the study within a range of 1-10 mcg/kg in order to maintain platelet counts between 50 and 200 x 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 mcg/kg (25th-75th percentile respectively; median 3 mcg/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 (≥ grade 3) bleeding events occurred at platelet counts $< 30 \times 10^9$/L. All bleeding events ≥ 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 romiplostim 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 waived the obligation to submit data for children < 1 year.

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies. Study S5 (20080279) was a phase 3 study with 24 weeks of romiplostim treatment and study S6 (20060195) was a phase 1/2 study with 12 weeks of romiplostim treatment (up to 16 weeks for eligible responders who enter a 4-week pharmacokinetic assessment period).

Both studies enrolled paediatric subjects (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of 2 platelet counts $\leq 30 \times 10^9$/L with neither count $> 35 \times 10^9$/L in both studies) with ITP, regardless of splenectomy status.

In study S5, 62 subjects were randomised in a 2:1 ratio to receive romiplostim (n = 42) or placebo (n = 20) and stratified into 1 of 3 age cohorts. The starting dose of romiplostim 1 mcg/kg and doses were adjusted to maintain (50 to 200 x 10^9/L) platelet counts. The most frequently used weekly dose was 3-10 mcg/kg and the maximum allowed dose on study was 10 mcg/kg. Patients received single subcutaneous weekly injections for 24 weeks. Of those 62 subjects, 48 subjects had ITP > 12 months of duration (32 subjects received romiplostim and 16 subjects received placebo).

The primary endpoint was the incidence of durable response, defined as achieving at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment. Overall, a significant greater proportion of subjects in the romiplostim arm achieved the primary endpoint compared with subjects in the placebo arm (p = 0.0018). A total of 22 subjects (52%) had durable platelet response in the romiplostim arm compared with 2 subjects (10%) in the placebo arm: ≥ 1 to < 6 years 38% versus 25%; ≥ 6 to < 12 years 56% versus 11%; ≥ 12 to < 18 years 56% versus 0.

In the subset of subjects with ITP > 12 months of duration, the incidence of durable response was also significantly greater in the romiplostim arm compared with the placebo arm (p = 0.0022). A total of 17 subjects (53.1%) had durable platelet response in the romiplostim arm compared with 1 subject (6.3%) in the placebo arm: ≥ 1 to < 6 years 28.6% versus 25%; ≥ 6 to < 12 years 63.6% versus 0%; ≥ 12 to < 18 years 57.1% versus 0%.

The composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event. The mean (SD) number of composite bleeding episodes was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.5 (0, 4.5) in the placebo arm. In the subset of subjects with ITP > 12 months of duration, the mean (SD) number of composite bleeding episodes was 2.1 (4.7) for the romiplostim arm and 4.2 (7.5) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.0 (0, 4) in the placebo arm. Because the statistical testing for the incidence of rescue medication use was not significant, no statistical test was done for the number of composite bleeding episodes endpoint.

In study S6, 22 subjects were randomised in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 mcg/kg every 2 weeks and the target platelet count was ≥ 50 x 10^9/L. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0008). Of those 22 subjects, 17 subjects had ITP > 12 months of duration (14 subjects received romiplostim and 3 subjects received placebo). Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0147).

Paediatric subjects who had completed a prior romiplostim study (including study S5) were allowed to enrol in study S7 (20090340), an open-label extension study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic paediatric subjects with ITP.

A total of 66 subjects were enrolled in this study, including 54 subjects (82%) who had completed study S5. Of these, 65 subjects (98.5%) received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg). Of the 66 subjects enrolled in the study, 63 subjects had ITP > 12 months of duration. All the 63 subjects received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 138.0 weeks (91.1 weeks, 186.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg).

Across the study, the overall subject incidence of platelet response (1 or more platelet count ≥ 50 x 10^9/L in the absence of rescue medication) was 93.8% (n = 61) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 34.0 months (24.0 months, 46.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

In the subset of subjects with ITP > 12 months of duration, the overall subject incidence of platelet response was 93.7% (n = 59) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 35.0 months (23.0 months, 47.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

A total of 31 subjects (47.7%) used concurrent ITP therapy during the study including 23 subjects (35.4%) who used rescue medication and 5 subjects (7.7%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 30.8% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

In the subset of subjects with ITP > 12 months of duration, 29 subjects (46.0%) used concurrent ITP therapy during the study including 21 subjects (33.3%) who used rescue medication and 5 subjects (7.9%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 31.7% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

The subject prevalence of rescue medication use showed a trend towards a reduction over the course of the study: from 24.6% (weeks 1 to 12) to < 13.0% (weeks 13 to 216), then 0% after week 216 until the end of the study. Similar reduction of the subject prevalence of rescue medication over the course of the study was seen in the subset of subjects with ITP > 12 months of duration: from 25.4% (weeks 1 to 12) to ≤ 13.1% (weeks 13 to 216), then 0% after week 216 until the end of the study.

Study S8 (20101221) was a phase 3, long-term, single-arm, open-label, multicentre study conducted in 203 paediatric patients with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies. Romiplostim was administered weekly by subcutaneous injection starting at a dose of 1 mcg/kg with weekly increments to a maximum dose of 10 mcg/kg to reach a target platelet count between 50 x 10^9/L and 200 x 10^9/L. The median age of the patients was 10 years (range, 1 to 17 years) and the median duration of treatment were 155.9 (range, 8.0 to 163.0) weeks.

The mean (SD) and median percentage of time with a platelet response (platelet count ≥ 50 x 10^9/L) within the first 6 months of initiation of romiplostim without rescue medication use for the past 4 weeks was 50.57% (37.01) and 50.0%, respectively. Sixty (29.6%) subjects overall received rescue medications. Rescue medications (i.e., corticosteroids, platelet transfusions, IVIG, azathioprine, anti-D immunoglobulin, and danazol) were permitted.

Study S8 also evaluated bone marrows for reticulin and collagen formation as well as for abnormalities in paediatric patients with ITP receiving romiplostim treatment. The modified Bauermeister grading scale was used for reticulin and collagen assessments, whereas cytogenetics and fluorescence *in situ* hybridization (FISH) were used to evidence bone marrow abnormalities. Based on cohort assignment at the time of study enrolment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1) or year 2 (cohort 2) in comparison to the baseline bone marrow at the start of the study. From the total of 79 patients enrolled in the 2 cohorts, 27 of 30 (90%) patients in cohort 1 and 36 of 49 (73.5%) patients in cohort 2 had evaluable on-study bone marrow biopsies. Increased reticulin fibre formation was reported for 18.5% (5 of 27) of patients in cohort 1 and 47.2% (17 of 36) of patients in cohort 2. No patients in either cohort developed collagen fibrosis or a bone marrow abnormality that was inconsistent with an underlying diagnosis of ITP.

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 mcg/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 mcg/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 mcg/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 removed from the refrigerator for a period of 30 days at room temperature (up to 25°C) when stored in the original carton.

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

6.5 Nature and contents of container

Powder:

5 mL single-dose 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 mcg of romiplostim can be delivered (see vial content table below).

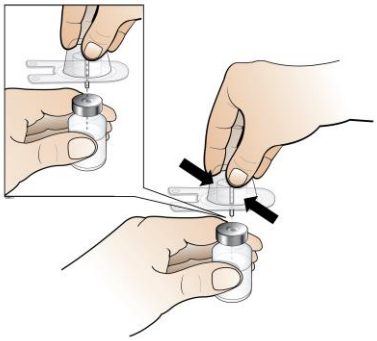
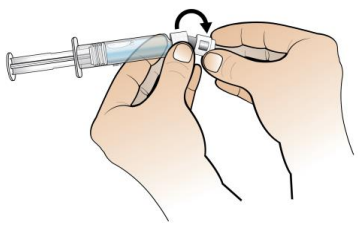
Nplate 500 micrograms powder and solvent for solution for injection

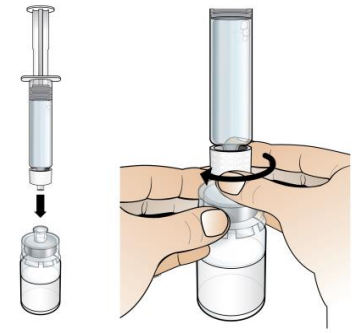
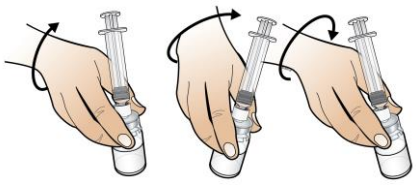
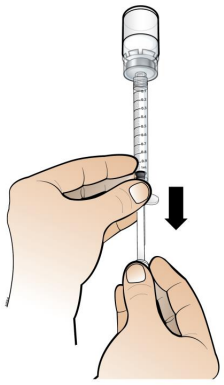
Nplate 500 micrograms powder for solution for injection should be reconstituted with 1.2 mL sterile water for injections, yielding a deliverable volume of 1 mL. An additional overfill is included in each vial to ensure that 500 mcg of romiplostim can be delivered (see vial content table below).

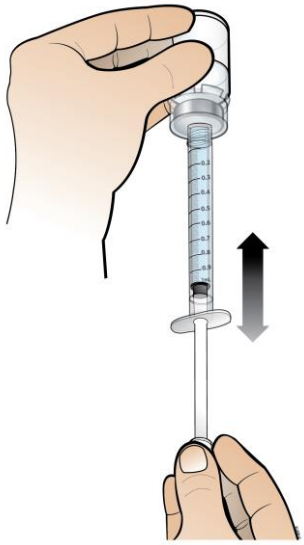
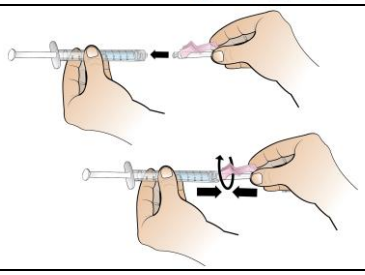
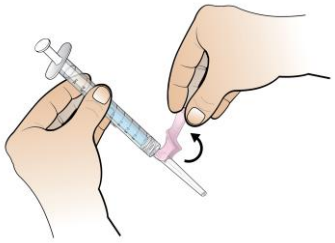
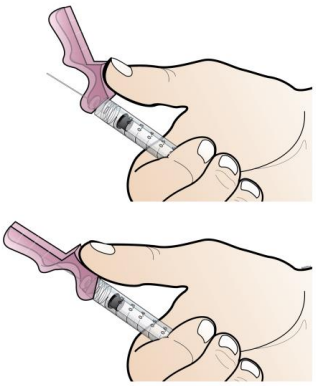
Vial Content:

Nplate single-use vial	**Total vial content of romiplostim**		**Volume of sterile water for injection**		**Deliverable product and volume**	**Final concentration**
250 mcg	375 mcg	+	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL
500 mcg	625 mcg	+	1.20 mL	=	500 mcg in 1.00 mL	500 mcg/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.

1.	Remove the plastic cap from Nplate powder vial and clean rubber stopper using the provided alcohol swab.	
2.	Attach vial adapter to Nplate vial by peeling off **paper backing from vial adapter, keeping the vial adapter in its packaging.** Keeping the **vial on the bench,** push the vial adapter down onto the centre of the vial until it is firmly in place. **Note: To prevent contamination of the product, do not touch the vial adapter spike or Luer lock.**	
3.	**Remove and discard vial adapter packaging.**	
4.	**Attach plunger rod to the pre-filled syringe of water for injections** by twisting the plunger rod clockwise onto the syringe plunger, until you feel a slight resistance.	
5.	**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.**	

6.	**Keeping the vial on the bench, attach the pre-filled syringe of water for injections to vial adapter:** 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.	
7.	**<u>Very slowly and gently expel all water</u>** 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. **<u>Do not</u>** <u>shake the vial</u> **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.**	 **Note:** This may take up to 2 minutes for the powder to completely dissolve.
Before continuing: **Do** visually inspect the reconstituted solution for particulate matter and/or discolouration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discolouration are observed. **Do** make sure solution is fully dissolved before removing syringe.		
8.	Remove the empty pre-filled syringe from the vial adapter.	
9.	**Remove 1 mL administration syringe from package. Attach the 1 mL syringe to** vial adapter of <u>reconstituted solution</u> by twisting the syringe tip onto the vial adapter until you feel a slight resistance.	
10.	**Turn assembled syringe-vial unit upside down,** so the vial of reconstituted product is above the syringe. **Withdraw all** of the medicinal product solution into the administration syringe. **Do** ensure that the plunger remains in the syringe.	

11.	**Ensure the correct amount of solution** for the patient dose is in the administration syringe by injecting any excess solution back into the vial. **Note: Remove all air bubbles from syringe to ensure precise solution amount is in syringe.**	
12.	**Twist off administration syringe from vial adapter.** **Attach safety needle** to the filled administration syringe by twisting needle **clockwise** into syringe Luer lock tip.	
13.	Prepare injection site with a new alcohol swab. **Pull back on the pink safety cover** toward the syringe and away from the needle. **Remove clear needle shield from prepared needle** by holding syringe in one hand and carefully pulling shield straight off with the other hand.	
14.	**Administer subcutaneous injection** following local protocols and good aseptic technique.	
15.	**After injecting, activate the pink safety cover** by pushing the cover forward using the same hand until you hear and/or feel it click/lock.	
16.	**Immediately discard syringe and needle** into an approved Sharps Container.	

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 LLC
State Road 31,
Km 24.6,
Juncos,
Puerto Rico 00777
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) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

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 (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs 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 marketing authorisation holder (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 as a guide to the correct reconstitution, dilution (if required) 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.
- As self-administration of Nplate is not allowed for paediatric patients, the HAT pack is intended for use with adult patients and not with paediatric patients.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nplate 125 micrograms powder for solution for injection
romiplostim

2. STATEMENT OF ACTIVE SUBSTANCE

Vial containing 125 micrograms of romiplostim. After reconstitution, a deliverable volume of 0.25 mL solution contains 125 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/1/08/497/009
EU/1/08/497/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nplate 125 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Nplate 125 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

125 µg

6. OTHER

Amgen Europe B.V.

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nplate 250 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nplate 500 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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

6. OTHER

For 250 µg kit

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 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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

1.2 ml

6. OTHER

For 500 µg kit

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nplate 125 micrograms powder for solution for injection
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

Nplate's active ingredient is romiplostim, which is a protein used to treat low platelet counts in patients with immune primary thrombocytopenia (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 with ITP who may or may not have had their spleen removed and who have been previously treated with corticosteroids or immunoglobulins, where these treatments don't work. Nplate is also used to treat children aged 1 year and over with chronic ITP who may or may not have had their spleen removed 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 (≥ 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 aged under 1 year.

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

Adult and children (1 to 17 years):

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.

Children (1 to 17 years old): in addition to adjusting your dose based on platelet counts, your doctor will also regularly reassess your body weight in order to adjust your dose.

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.

Possible side effects in adults with ITP

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;
- inflammation of the sinuses (sinusitis);
- inflammation of the passages that carry air to the lungs (bronchitis);
- blood clot in the veins (deep vein thrombosis).

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 (hypoaesthesia); 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); 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 (leucocytosis);
- 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.

Possible side effects in children with ITP

Very common: may affect more than 1 in 10 people
- upper respiratory tract infection;
- pain in the mouth and throat (oropharyngeal pain);
- itchy, runny or blocked nose (rhinitis);
- cough;
- upper abdominal pain;
- diarrhoea;
- rash;
- fever (pyrexia);
- bruising (contusion).

Common: may affect up to 1 in 10 people
- gastroenteritis;
- sore throat and discomfort when swallowing (pharyngitis);
- inflammation of the eye (conjunctivitis);
- ear infection;
- inflammation of the sinuses (sinusitis);
- swelling in the limbs/hands/feet;
- bleeding beneath the surface of the skin or bruising under the skin (purpura);
- itchy rash (urticaria).

Uncommon: may affect up to 1 in 100 people
- higher than normal platelet counts (thrombocytosis).

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 period of 30 days at room temperature (up to 25°C) when stored in the original carton.

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 125 micrograms powder for solution for injection contains a total of 230 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 125 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 0.25 mL solution contains 125 micrograms of romiplostim (500 micrograms/mL).

  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 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 single-dose glass vial.

Carton containing 1 or 4 vials of either 125 micrograms (beige cap), 250 micrograms (red cap) or 500 micrograms of romiplostim (blue cap).

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.
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The Netherlands

Manufacturer
Amgen Technology (Ireland) Unlimited Company
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Manufacturer
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Telecomlaan 5-7
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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

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The following information is intended for healthcare professionals only:

Reconstitution:

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 125 micrograms powder for solution for injection** should be reconstituted with 0.44 mL sterile water for injections, yielding a deliverable volume of 0.25 mL. An additional over fill is included in each vial to ensure that 125 mcg of romiplostim can be delivered (see vial content table below).

or

- **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 mcg 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 mcg 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**
125 mcg	230 mcg	+	0.44 mL	=	125 mcg in 0.25 mL	500 mcg/mL
250 mcg	375 mcg	+	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL
500 mcg	625 mcg	+	1.20 mL	=	500 mcg in 1.00 mL	500 mcg/mL

Sterile water for injections only should be used when reconstituting the medicinal product. 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 discolouration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discolouration 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.

Dilution (required when the calculated individual patient dose is less than 23 mcg)

Initial reconstitution of romiplostim with designated volumes of sterile water for injections results in a concentration of 500 mcg/mL in all vial sizes. If the calculated individual patient dose is less than 23 mcg, an additional dilution step to 125 mcg/mL with **preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection** is required to ensure accurate volume (see table below).

Dilution Guidelines:

Nplate single-use vial	Add this volume of preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection to the **reconstituted vial**	Concentration after dilution
125 mcg	1.38 mL	125 mcg/mL
250 mcg	2.25 mL	125 mcg/mL
500 mcg	3.75 mL	125 mcg/mL

Preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection only must be used for dilution. Dextrose (5%) in water or sterile water for injection should not be used for the dilution. No other diluents have been tested.

From a microbiological point of view, the diluted 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 4 hours at 25°C in disposable syringes, or 4 hours in a refrigerator (2°C – 8°C) in the original vials, protected from light.

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

Nplate's active ingredient is romiplostim, which is a protein used to treat low platelet counts in patients with immune primary thrombocytopenia (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) with ITP who may or may not have had their spleen removed 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 (≥ 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 anti-platelet 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 (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;
- inflammation of the sinuses (sinusitis);
- inflammation of the passages that carry air to the lungs (bronchitis);
- blood clot in the veins (deep vein thrombosis).

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 (hypoaesthesia); 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); 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 (leucocytosis);
- 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 period of 30 days at room temperature (up to 25°C) when stored in the original carton.

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 single-dose 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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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

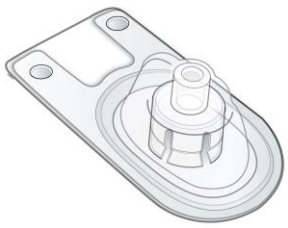
Do the following:

- 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, 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:**

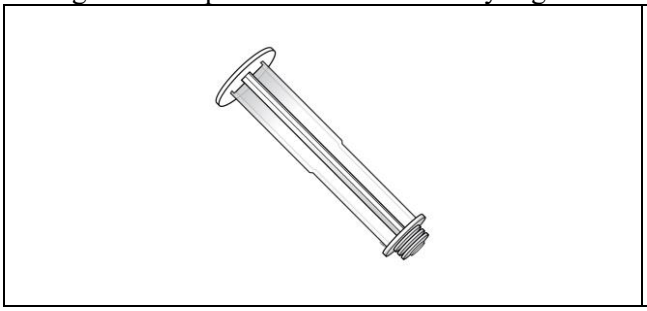
Alcohol swab package **x4**

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**
	

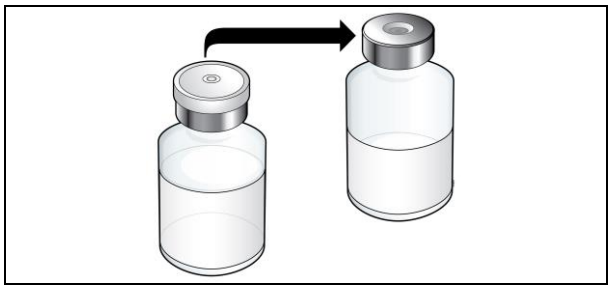
- **Do not** open items until directed in instructions.
- **Do not** use components that have evidence of tampering or damage.
- **Do not** re-use items.

Step 2. Prepare vial for use, attach vial adapter

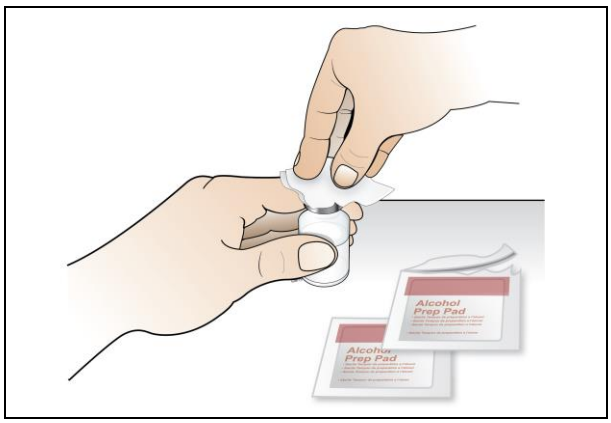
Using: 2 alcohol swab packages, 1 vial, and 1 vial adapter package.

Do the following:

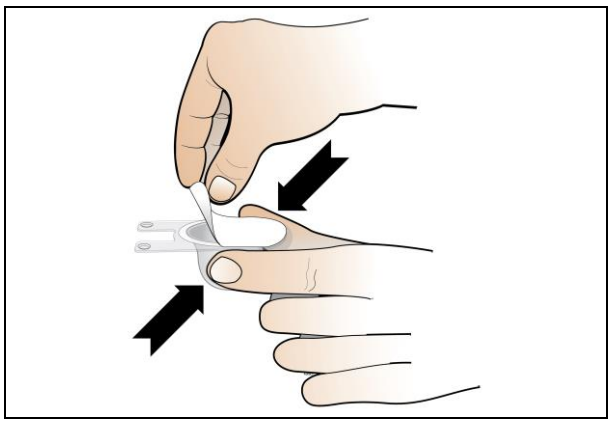
- **Wash your hands** with soap and warm water.
- **Clean the flat work surface with a new alcohol swab.**
- **Remove red (250 micrograms) or blue (500 micrograms) plastic cap from vial.**



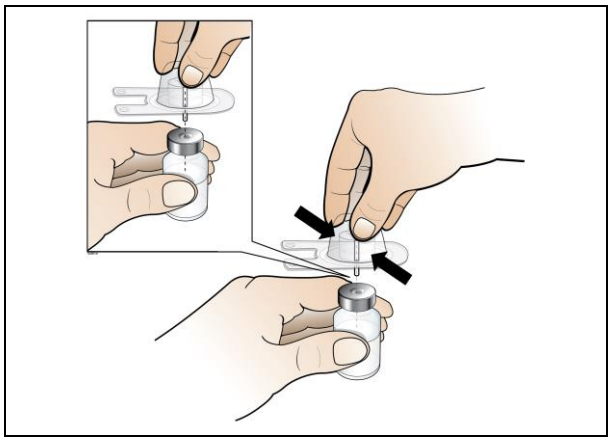
- Using a new alcohol swab **clean vial stopper.**
- **Do not** touch vial stopper after cleaning it.



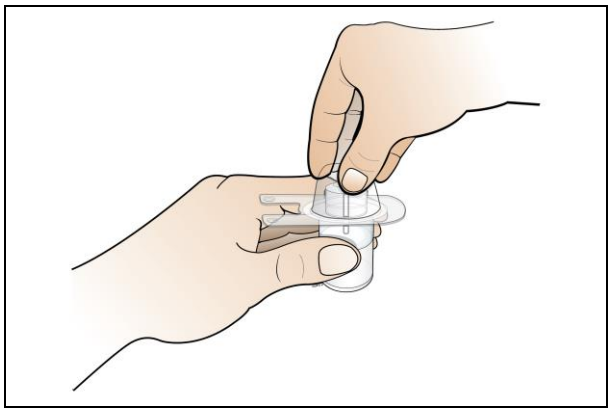
- **Peel off paper backing slowly from vial adapter while keeping vial adapter in the plastic package.**
- **Do not** touch vial stopper or spike of vial adapter.



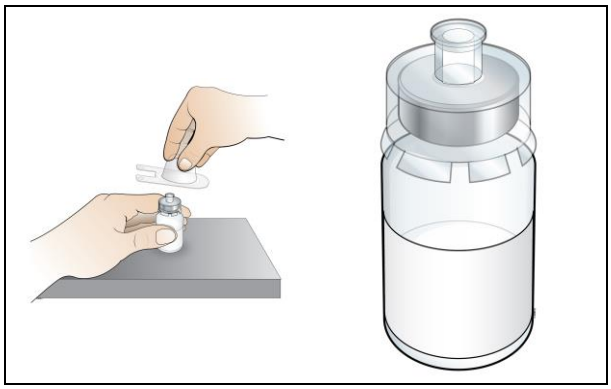
- Keeping the **vial on a table,** and keeping the vial adapter in the plastic packaging, **line up spike on the vial adapter to the centre of the stopper on the vial.**



- **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

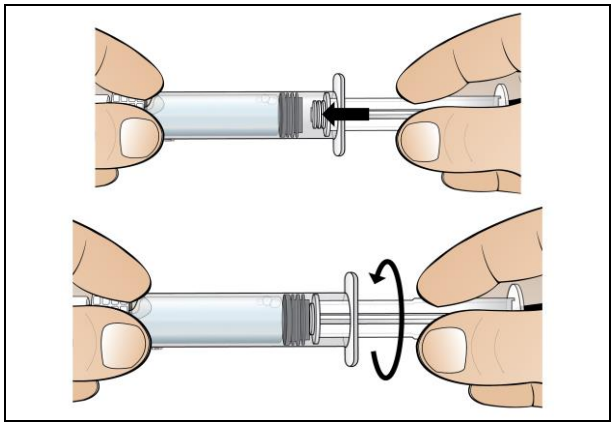
Using: Pre-filled sterile water syringe and plunger rod.

Before you begin Step 3 please note the following:

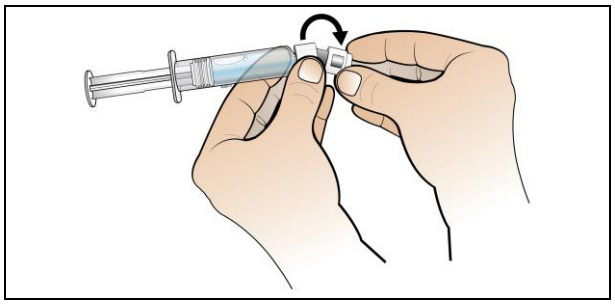
- The clear plastic plunger rod MUST always be attached first before breaking the white tip off of the pre-filled water syringe. Perform step 3a before step 3b.

Do the following:

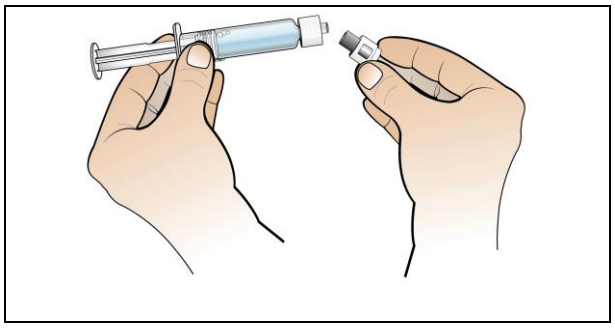
- **Step 3a: Attach clear plastic plunger rod to pre-filled sterile water syringe** by placing the threaded end of the plunger rod into the syringe and carefully twisting the rod clockwise onto the grey syringe plunger, until you feel a slight resistance. Do not over tighten.



- **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

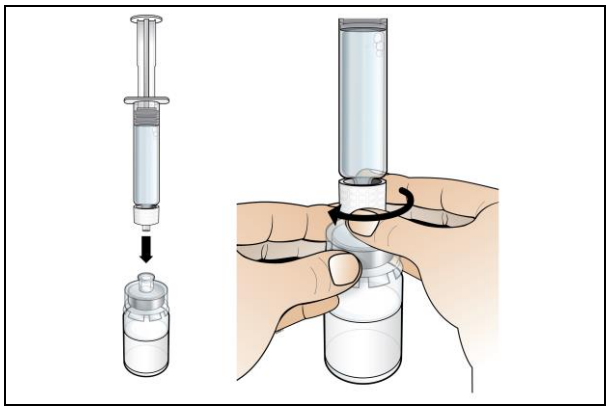
Using: Pre-filled sterile water syringe and vial with vial adapter attached.

Before you begin Step 4 please note the following:

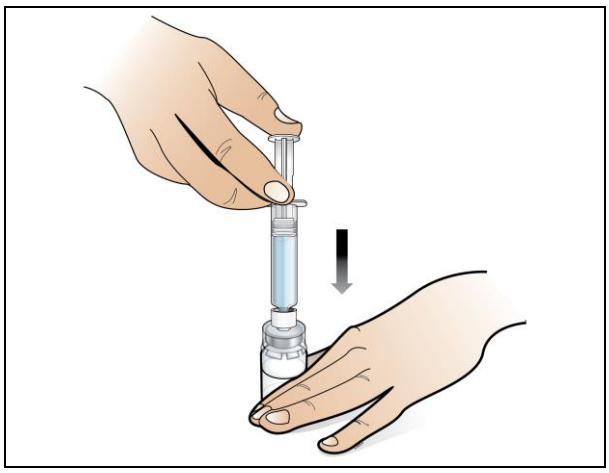
- **Do** dissolve slowly and carefully. This is a protein product and proteins can be easily damaged by improper mixing and excessive shaking.

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.

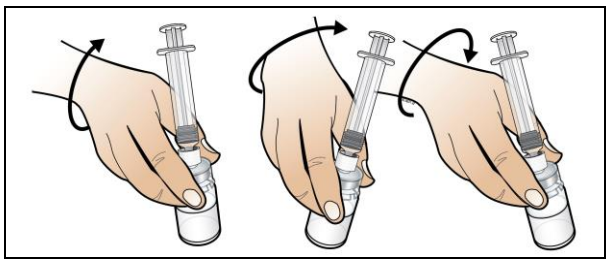


Push slowly and gently

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.**



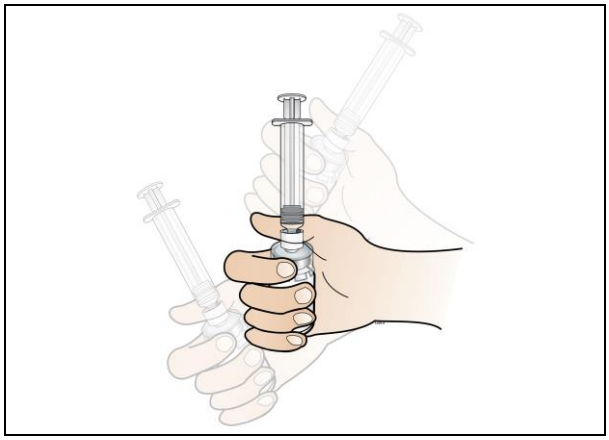
Correct

- **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

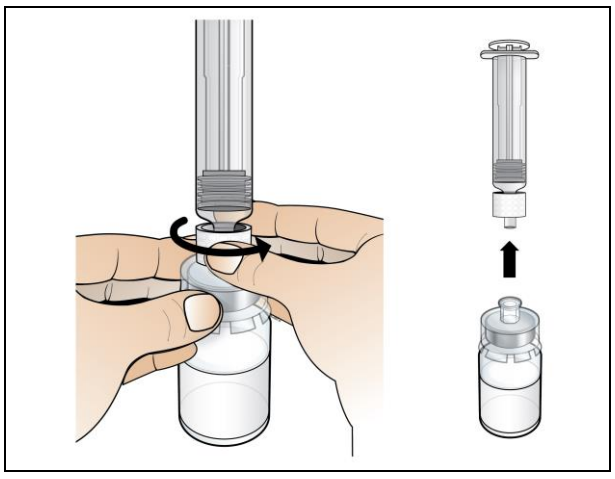
Before continuing:

- **Do** visually inspect the dissolved liquid for particles and/or discolouration. 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

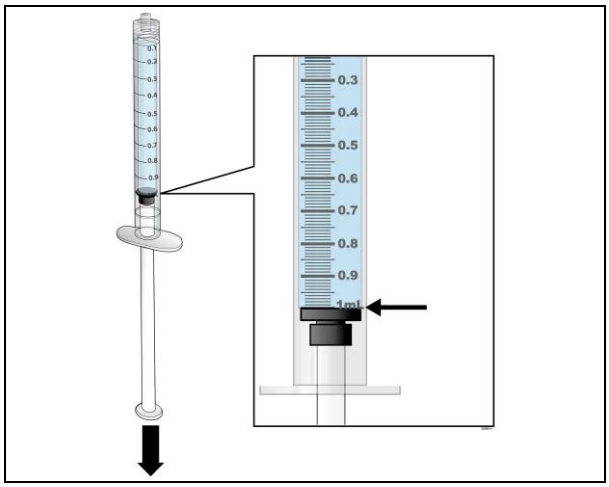
Using: A new 1 mL syringe package and the vial of dissolved, clear Nplate.

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.

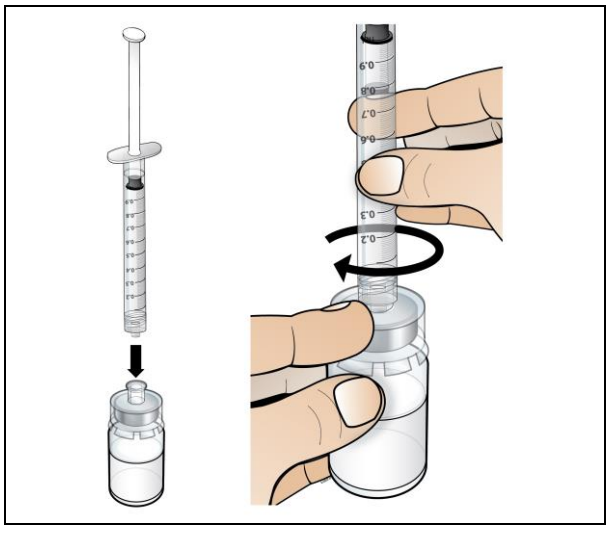
Do the following:

- **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

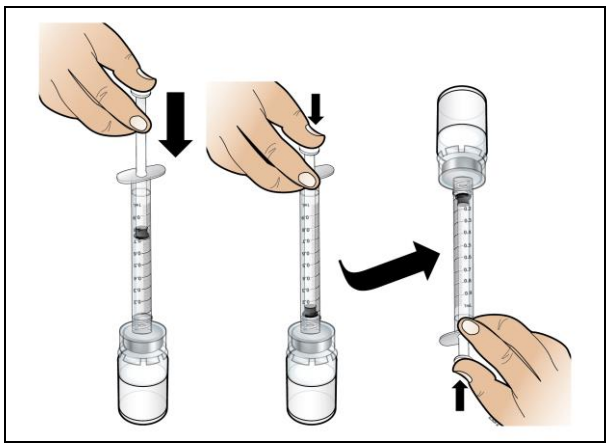
- **Attach 1 mL syringe to vial adapter** of the dissolved Nplate by twisting the syringe tip clockwise onto the vial adapter until you feel a slight resistance.



A. **Push air into vial.**

B. **Maintain pressure on plunger.**

C. **Turn vial assembly and syringe upside down,** so the vial is directly above the syringe.



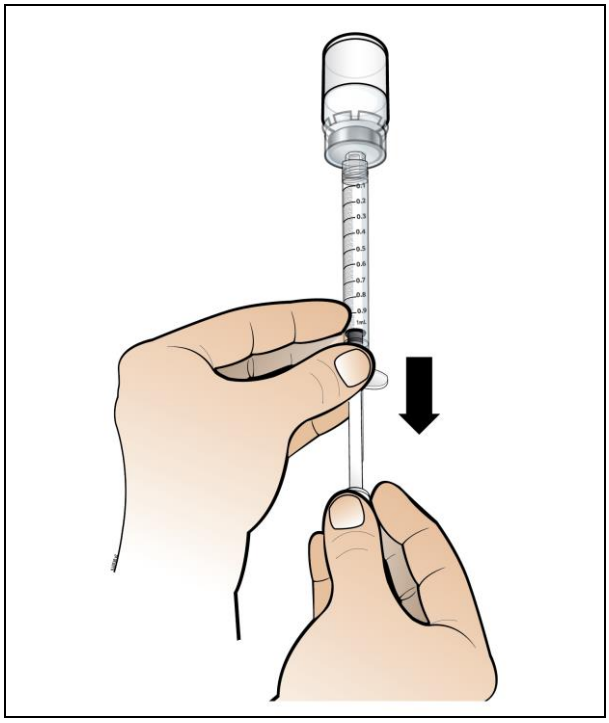
A. **B.** **C.**

Flip

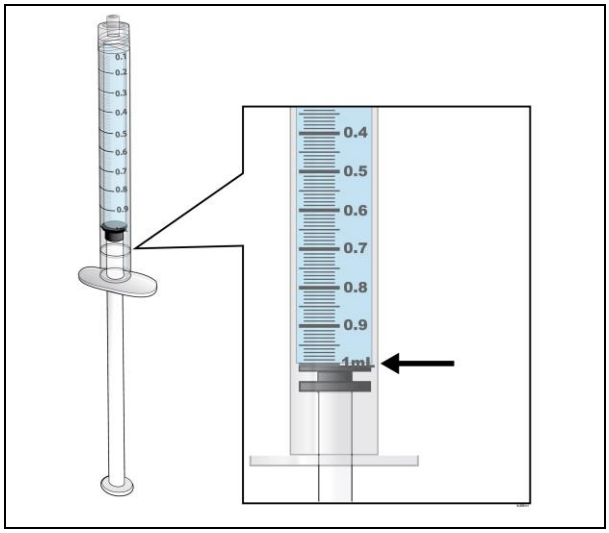
- **Withdraw the full amount of liquid into the syringe.**

  - 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.

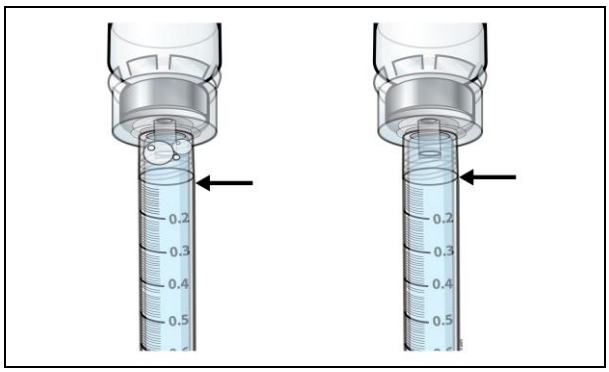


- **Do** ensure that the plunger remains in the syringe.



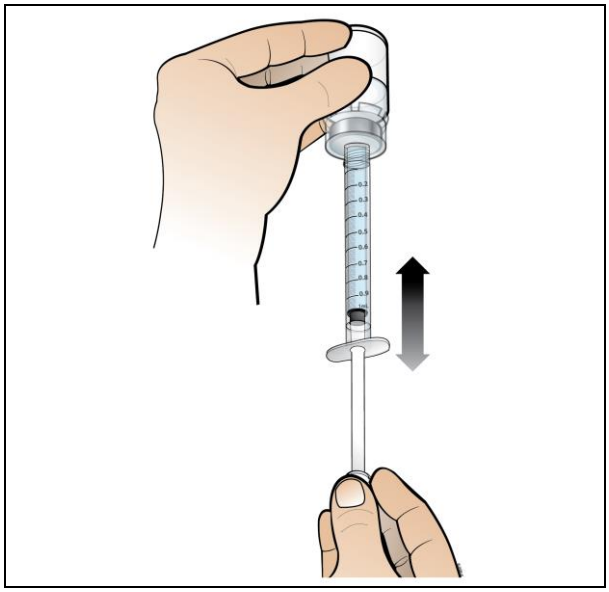
Correct

- **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.



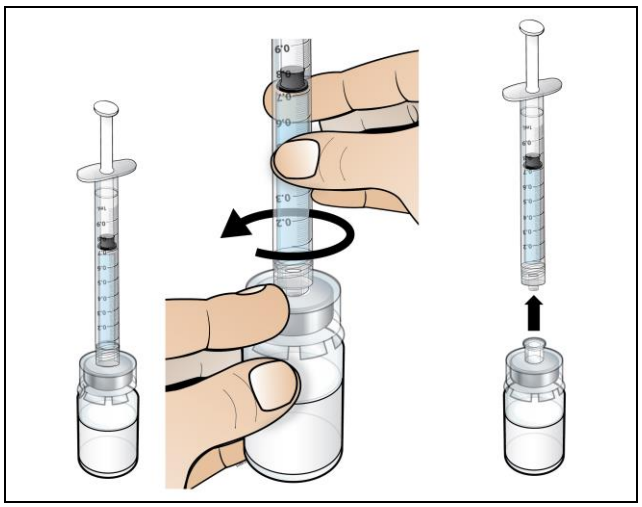
Adjust the amount to your prescribed dose

- **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.

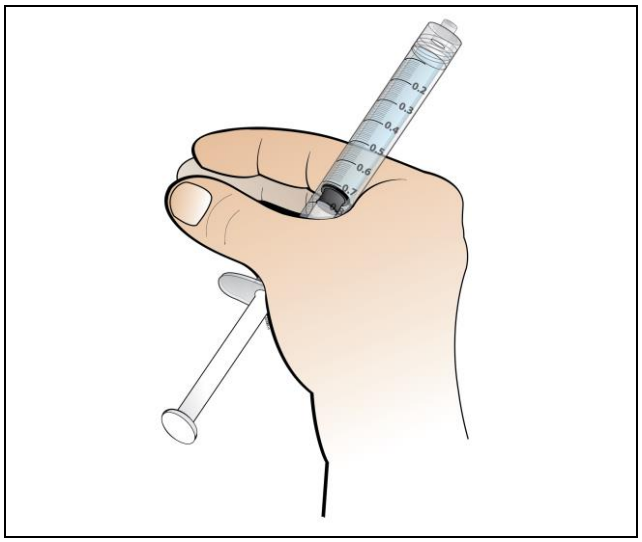
Before continuing:

- **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.

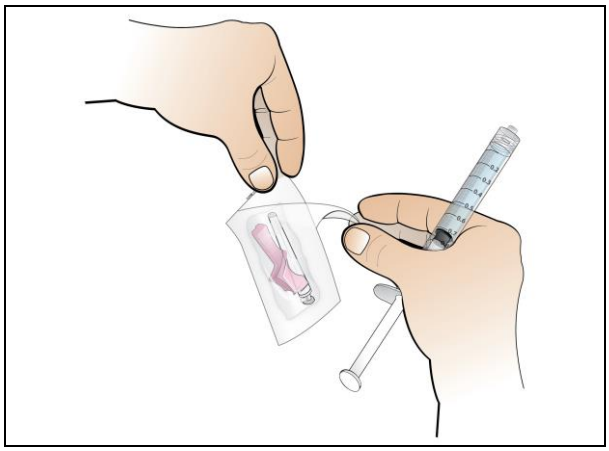


Step 6. Prepare injection needle

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

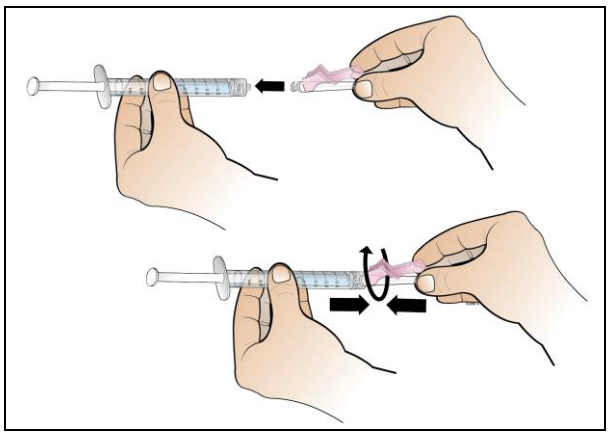
Do the following:

- 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.

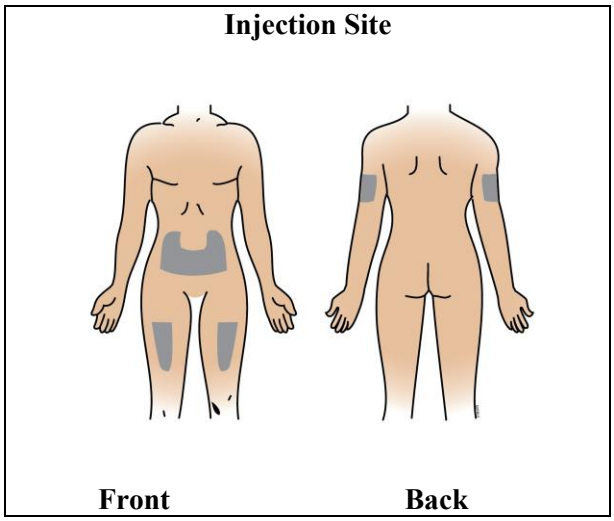


Step 7. Choose and prepare an injection site

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.

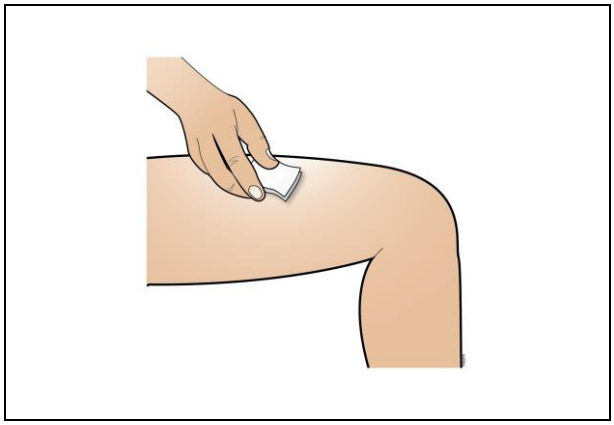


- **Do not inject into areas where the skin is tender, bruised and hard.**

- **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.

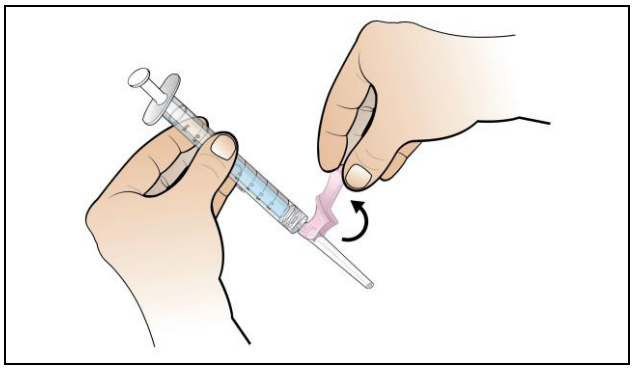


Step 8. Injecting the Nplate liquid

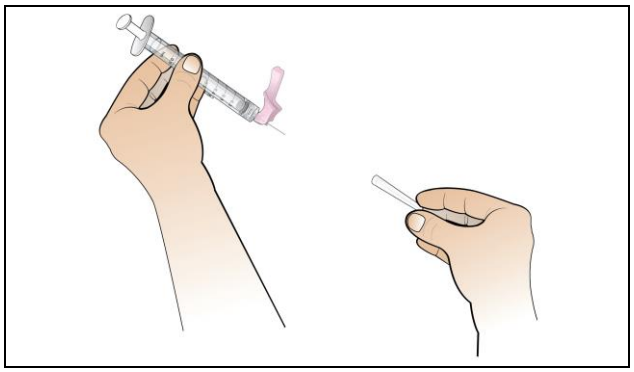
Using: Filled syringe and needle assembly.

Do the following:

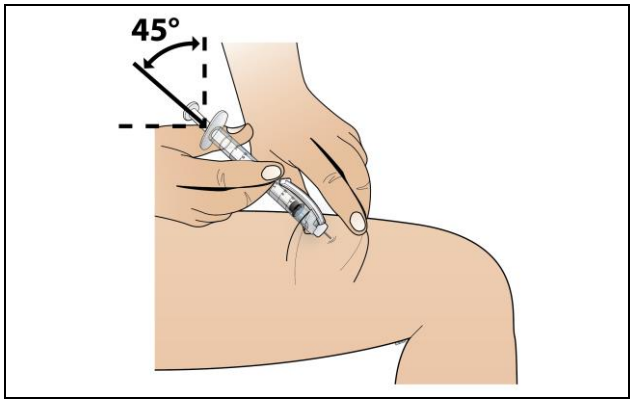
- **Pull back on the pink safety cover** (toward the syringe and away from the needle).



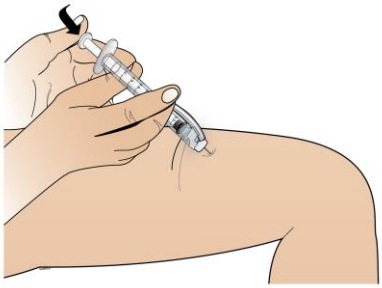
- **Remove clear needle shield** by holding syringe in one hand and carefully pulling shield straight off with the other hand.
- **Do** remove the clear needle shield before injecting.



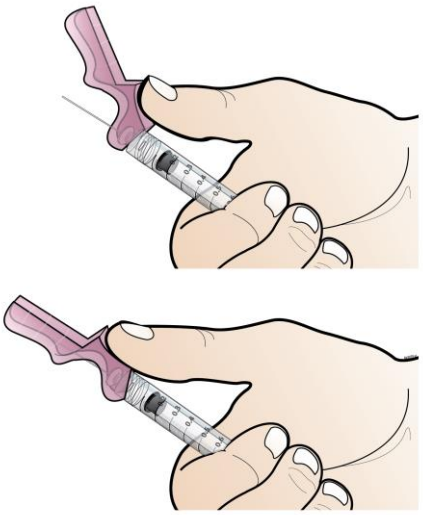
- With one hand, **gently pinch** the **cleaned area** of skin and hold it firmly. With the other hand, **hold the syringe (like a pencil) at a 45-degree angle** to the skin.
- With a short, sharp motion, **push the needle into the skin.**



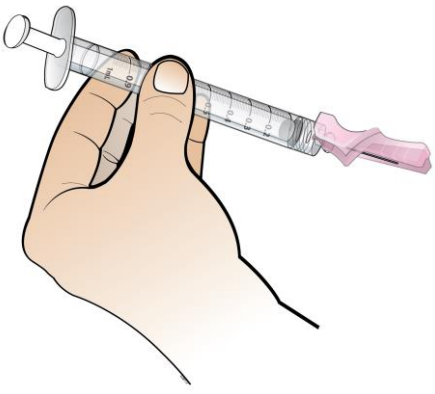
- Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.
- When the syringe is empty, pull the needle out of the skin, **being careful to keep it at the same angle as inserted.**
- There may be a little bleeding at the injection site. You can press a cotton ball or 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.**