Professional Information

**SCHEDULING STATUS:** S4

## 1. NAME OF MEDICINE

NPLATE 250 µg (Powder for solution for injection)

NPLATE 500 µg (Powder for solution for injection)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NPLATE 250 µg powder for solution for injection:

Each vial contains 250 µg of romiplostim. After reconstitution, a deliverable volume of 0,5 ml solution contains 250 µg of romiplostim (500 µg/ml). An additional overfill is included in each in each vial to ensure that 250 µg of romiplostim can be delivered.

NPLATE 500 µg powder for solution for injection:

Each vial contains 500 µg of romiplostim. After reconstitution, a deliverable volume of 1,0 ml solution contains 500 µg of romiplostim (500 µg/ml). An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered.

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

Contains sugar (sucrose and mannitol).

For full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Powder for solution for injection. NPLATE is a white solid cake.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

NPLATE is indicated for immune thrombocytopenia

(ITP) patients 1 year of age and older who are refractory to other treatments

(e.g. corticosteroids, immunoglobulins) (see section 4.2 and 5.1).

**4.2 Posology and Method of Administration**

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

**Posology:**

NPLATE should be administered subcutaneously. The recommended initial dose for NPLATE is 1 µg/kg based on actual body weight, administered once weekly as a subcutaneous injection. The dose should be adjusted so patients achieve and maintain their platelet counts within a recommendation platelet range of 50 x $10^9$/l to 200 x $10^9$/l.

*Dosage Calculation*

The volume administered is calculated based on body weight, dose required and concentration of product

Guidelines for calculating individual patient dose and volume of NPLATE to administer

| | |
|---|---|
| Individual patient dose | Individual patient dose (µg) = weight (kg) x dose in µg/kg<br>Actual body weight at initiation of treatment should always be used when calculating initial dose.<br>• In adults, future dose adjustments are based on changes in platelet counts only.<br>• In paediatric patients, future dose adjustments are based on changes in platelet counts and changes in body weight. |

| | |
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| | Reassessment of body weight is recommended every 12 weeks. |
| If individual patient dose ≥ 23 µg | Reconstitute lyophilised product as described in section Instructions on reconstitution of NPLATE.<br>The resulting concentration is 500 µg/ml.<br>Volume to Administer (ml) = Individual patient Dose (µg) / 500 µg/ml (Round volume to the nearest hundredth ml) |
| If Individual Patient Dose < 23 µg | Dilution is required to ensure accurate dosing.<br>Reconstitute lyophilised product as described in Section Instructions on reconstitution of NPLATE and then dilute the product as described in Section Instructions on reconstitution of NPLATE. The resulting concentration is 125 µg/ml.<br>Volume to Administer (ml) = Individual patient Dose (µg) / 125 µg/ml (Round volume to the nearest hundredth ml) |
| Example | 10 kg patient is initiated at 1 µg/kg of NPLATE.<br>Individual patient dose (µg) = 10 kg x 1 µg/kg = 10 µg<br>Because the dose is < 23 µg, dilution is required to ensure accurate dosing. Reconstitute lyophilised product as described in Section Instructions on reconstitution of NPLATE and then dilute the product as described in Section Instructions on reconstitution of NPLATE. The resulting concentration is 125 µg/ml.<br>Volume to Administer (ml) = 10 µg / 125 µg/ml = 0,08 ml |

Dose adjustments

The recommended initial dose for NPLATE is 1 µg/kg based on actual body weight, administered once weekly as a subcutaneous injection. The dose should be adjusted so, patients achieve and maintain their platelet counts within a recommendation

platelet range of 50 x $10^9$/l to 200 x $10^9$/l.

Adults:

In the placebo-controlled studies (Study 1 and Study 2 ), the most frequently used weekly dose for splenectomised patients was between 2 - 7 µg/kg ($25^{th}$ - $75^{th}$ percentile respectively; median 3 µg/kg) and for nonsplenectomised patients was Between 1 - 3 µg/kg ($25^{th}$ - $75^{th}$ percentile respectively; median 2 µg/kg) 11,12. The maximum dose of 10 µg/kg should not be exceeded.

Paediatrics:

In the placebo-controlled study (Study 5), the most frequently used weekly dose was 3 - 10 µg/kg ($25^{th}$ - $75^{th}$ percentile respectively; median 5,5 µg/kg). The maximum dose of 10 µg/kg should not be exceeded.

Dose adjustments should be based on platelet counts measured weekly until stable within the recommended range.

Thereafter, platelet counts should be measured at least monthly and appropriate dose adjustments made as per the Dose Adjustment Table for Adult Patients (Table 1) or Dose Adjustment Table for Paediatric Patients (Table 2) in order to maintain platelet counts within the recommended range.

See below tables for dose adjustment and monitoring.

**Table 1:** Adult Dose Adjustment Guidance Based on Platelet Count

| Platelet Count (x $10^9$/l) | Action | Adjustment Frequency |
|---|---|---|
| **Initial dose is 1 µg/kg, based on actual body weight** | | |
| < 50 | Increase dose in 1 µg/kg increments. | Every week |

| | | |
|---|---|---|
| 50 to 400 | Adjust dose in 1 µg/kg increments (increase or decrease) at the physician's discretion to achieve a recommended platelet count between 50 and 200 x $10^9$/l. | Every 2 weeks |
| > 400 | Do not administer, stop scheduled dose. Reinitiate therapy when platelet count is < 200 x $10^9$/l. Consider decreasing the dose by 1 µg/kg on the next scheduled dosing day. Consider maintaining the dose of NPLATE if the platelet count increase was due to the initiation or increase in dose of a concurrently administered ITP | Every week |

If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of NPLATE.

If the patient loses response, see section 4.4:*Loss of response to NPLATE*.

Table 2: Paediatric dose adjustment guidance based on platelet count

| Platelet Count (x $10^9$/l) | Action | Adjustment Frequency |
|---|---|---|
| Initial dose is 1 µg/kg, based on actual body weight | | |
| < 50 | Increase dose in 1 µg/kg increments. | Every week |
| 50 to 200 | Dose remains constant | Every week |
| > 200 to < 400 for 2 consecutive weeks | Decrease dose by 1 µg/kg increments. | Every week |
| ≥ 400 | Do not administer, stop scheduled dose. Reinitiate therapy when platelet count is < 200 x $10^9$/l.<br>▪ Consider decreasing the dose by 1 µg/kg on the next scheduled dosing day.<br>▪ Consider maintaining the dose of NPLATE if the platelet count increase | Every week |

| | | |
|---|---|---|
| | was due to the initiation or increase in dose of a concurrently administered ITP medication. | |

If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of NPLATE.

If the patient loses response, see section 4.4: *Loss of response to NPLATE*.

Treatment Discontinuation

The reoccurrence of thrombocytopenia should be expected upon discontinuation of treatment (see section 4.4). Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician.

Discontinue romiplostim if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the highest weekly dose of 10 µg/kg.

Medical ITP therapies used in combination with romiplostim in clinical studies included corticosteroids, danazol, azathioprine, IVIG, and anti-D immunoglobulin. Corticosteroids, danazol, and azathioprine were reduced or discontinued when given in combination with romiplostim.

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

NPLATE should not be used in children aged under 1 year due to insufficient data on safety or efficacy.

Hepatic and renal impairment

Experience is limited in patients with severe hepatic or renal impairment. Romiplostim should be used with caution in these populations.

**Method of Administration**

NPLATE should be administered subcutaneously.

As the injection volume may be very small, use a syringe with graduations to 0,01 ml.

Administration precautions

Caution should be used during preparation of NPLATE in calculating the dose and reconstitution with the correct volume of Sterile Water for Injection (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 (see section 4,4).

For reconstitution Instructions (see section 6.6).

**4.3 Contraindications**

Hypersensitivity to romiplostim or to any of the excipients or to *E. coli*-derived proteins.

**4.4 Special Warnings and Precautions for use**

The following special warnings and precautions have been actually observed or are theoretical class effects of thrombopoietin (TPO) receptor stimulators.

Re-occurrence of thrombocytopenia and bleeding after cessation of treatment.

Thrombocytopenia is likely to re-occur upon discontinuation of treatment with NPLATE, thrombocytopenia of greater severity than was present prior to NPLATE may occur in adults and children. There is an increased risk for bleeding if NPLATE is discontinued in the presence of anticoagulants or anti- platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of treatment with NPLATE. Following discontinuation of NPLATE, obtain weekly complete blood counts (CBCs), including platelet counts, for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines. It is recommended that, if treatment with NPLATE is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

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 a peripheral blood smear and CBC prior to and during treatment with NPLATE are recommended.

See section 4.8 for information on the increases of reticulin observed in

NPLATE clinical trials.

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

Thrombotic/thromboembolic complications

Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. The incidences of thrombotic/thromboembolic events observed in the control groups were comparable to NPLATE in clinical studies.
An association between these events and elevated platelet counts was not observed. Dose adjustment guidelines should be followed (see section 4.2).

However, in the Post-marketing setting thrombotic/thromboembolic events have been observed (See section 4.8).

Progression of existing haematopoietic malignancies or Myelodysplastic Syndromes (MDS)

The risk-benefit profile for NPLATE has not been established in MDS or other non-ITP patient populations. TPO receptor stimulators are haematopoietic growth factors that lead to thrombopoietic progenitor cell expansion, differentiation, and receptor is predominantly expressed on the surface of cells of the myeloid lineage; platelet production. The TPO there is no confirmed expression of the TPO receptor

on solid tumours. For TPO receptor stimulators there is a theoretical concern that they may stimulate the progression of existing MDS.

In adult clinical studies of treatment with NPLATE in patients with MDS, there were reported cases of progression to acute myeloid leukaemia (AML), a potential clinical outcome of MDS. In addition, there were cases of transient blast cell increases, which did not progress to AML.

Loss of response to NPLATE

A loss of response or failure to maintain a platelet response with NPLATE 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 NPLATE on red and white blood cells

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

Sucrose

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal- absorption or sucrase-isomaltase insufficiency should not take NPLATE.

Contains mannitol and may have a laxative effect.

**4.5 Interaction with other medicines and other forms of interaction**

No interaction studies have been performed. The potential interactions of NPLATE with co-administered medicines due to binding to plasma proteins remain unknown. Medicines used in the treatment of ITP in combination with NPLATE in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG),and anti-D immunoglobulin. Platelet counts should be monitored when combining NPLATE with other medicines for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Dosage of corticosteroids, danazol, and azathioprine may be reduced or discontinued when given in combination with NPLATE (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

The safety and efficacy of NPLATE in pregnant women has not been established.

In rat and rabbit developmental toxicity studies, no evidence of foetal harm was observed at romiplostim exposures up to 11 times (rats) and 82 times (rabbits) higher than the maximum indicated human dose of 10 µg/kg (see section 4.2).
In mice, at exposures 5 times higher than the maximum indicated human dose, there were reductions in maternal body weight and evidence of increased post implantation loss.

In prenatal and postnatal development study in rats, at exposures 11 times the maximum indicated human dose, there was a slight increase in the incidence of

peri-natal pup mortality.

NPLATE is known to cross the placental barrier in rats at clinically relevant or higher doses.

NPLATE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

It is not known whether NPLATE is present in human milk. Many medicines are present in human milk and because of the potential for adverse effects in nursing infants from NPLATE, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the potential benefit of the medicine to the mother or the potential benefit of breastfeeding to the infant.

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**

*a) Summary of safety profile*

Based on an analysis of all adult ITP patients receiving NPLATE in 4 controlled and 5 uncontrolled clinical studies, the overall subject incidence of all adverse reactions for NPLATE-treated subjects was 91,5 % (248/271). The mean duration of exposure to NPLATE 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.

Patients also experienced symptoms consistent with anaphylaxis (see section on Adverse Reactions from Post-marketing Experience).

Adult population with ITP duration up to 12 months

The safety profile of NPLATE was similar across 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 NPLATE from among those patients in 9 ITP studies were included. 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 NPLATE patients with ITP duration up to 12 months, but were not observed in those adult patients with ITP duration > 12 months: bronchitis (8,3 %), sinusitis (5,4 %), vomiting (7,2 %).

*b) Tabulated list of adverse reactions*

Frequencies are defined as: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); Rare (≥ 1/10 000, < 1/1000); Very rare (< [≤] 1/ 10 000),including isolated reports. Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

| MedDRA | Very common | Common | Uncommon |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **system organ class** | | | |
| Infections and infestations | Upper respiratory tract infection<br>Rhinitis*** | Gastroenteritis<br>Pharyngitis***<br>Conjunctivitis***<br>Ear infection***<br>Sinusitis*** | Influenza<br>Localised infection<br>Nasopharyngitis |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | Multiple myeloma<br>Myelofibrosis |
| Blood and lymphatic system disorders | | Bone marrow disorder*<br>Thrombocytopenia*<br>Anaemia | Aplastic anaemia<br>Bone marrow failure<br>Leukocytosis<br>Splenomegaly<br>Thrombocythemia<br>Platelet count increased<br>Platelet count abnormal |
| Immune system disorder | Hypersensitivity** | Angioedema | |
| Metabolism and | | | Alcohol |

| | | | |
|---|---|---|---|
| nutrition disorders | | | intolerance<br>Anorexia<br>Decreased appetite<br>Dehydration<br>Gout |
| Psychiatric disorders | | Insomnia | Depression<br>Abnormal dreams |
| Nervous system disorders | Headache | Dizziness<br>Paraesthesia<br>Migraine | Clonus<br>Dysgeusia<br>Hypoaesthesia<br>Hypogeusia<br>Neuropathy peripheral<br>Transverse sinus thrombosis |
| Eye disorders | | | Conjunctival haemorrhage<br>Accommodation disorder<br>Blindness<br>Eye disorder<br>Eye pruritus<br>Lacrimation increased<br>Papilloedema<br>Visual Disturbances |
| Ear and labyrinth | | | Vertigo |

| | | | |
|---|---|---|---|
| disorders | | | |
| Cardiac disorders | | Palpitations | Myocardial infarction<br>Heart rate increased |
| Vascular disorders | | Flushing | Deep vein thrombosis<br>Hypotension<br>Peripheral embolism<br>Peripheral ischaemia<br>Phlebitis<br>Thrombophlebitis superficial<br>Thrombosis<br>Erythromelalgia |
| Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain*** | Pulmonary embolism* | Cough<br>Rhinorrhoea<br>Dry throat<br>Dyspnoea<br>Nasal congestion<br>Painful respiration |
| Gastrointestinal disorders | Upper abdominal pain*** | Nausea<br>Diarrhoea<br>Abdominal pain<br>Dyspepsia<br>Constipation | Vomiting<br>Rectal haemorrhage<br>Breath odour<br>Dysphagia<br>Gastro-oesophageal |

| | | | |
|---|---|---|---|
| | | | reflux disease<br>Haematochezia<br>Mouth haemorrhage<br>Stomach discomfort<br>Stomatitis<br>Tooth discolouration |
| Hepatobiliary disorders | | | Portal vein thrombosis<br>Increase in transaminase |
| Skin and subcutaneous tissue disorders | | Pruritus<br>Ecchymosis<br>Rash | Alopecia<br>Photosensitivity reaction<br>Acne<br>Dermatitis contact<br>Dry skin<br>Eczema<br>Erythema<br>Exfoliative rash<br>Hair growth abnormal<br>Prurigo<br>Purpura<br>Papular rash<br>Pruritic rash<br>Skin nodule<br>Abnormal skin odour<br>Urticaria |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia<br>Pain in extremity<br>Muscle spasm<br>Back pain<br>Bone pain | Muscle tightness<br>Muscular weakness<br>Shoulder pain<br>Muscle twitching |
| Renal and urinary disorders | | | Protein urine present |
| Reproductive system and breast disorders | | | Vaginal haemorrhage |
| General disorders and administration site conditions | | Fatigue<br>Peripheral oedema<br>Influenza-like-illness<br>Pain<br>Asthenia<br>Pyrexia<br>Chills<br>Injection site reaction<br>Peripheral swelling*** | Injection site haemorrhage<br>Chest pain<br>Irritability<br>Malaise<br>Face oedema<br>Feeling hot<br>Feeling jittery |
| Investigations | | | Increased blood pressure |

| | | | |
|---|---|---|---|
| | | | Increased blood lactate dehydrogenase<br>Increased body temperature<br>Decreased weight<br>Increased weight |
| 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

*c) Description of selected adverse reactions*

In addition, the events listed below have been deemed to be related to NPLATE 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 incidence of bleeding

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 NPLATE in 4 controlled and 5 uncontrolled clinical studies, 3 events of thrombocytosis were reported, n = 271. No clinical sequelae were reported in association with the elevated platelet counts in any of the 3 subjects.

Thrombocytosis in paediatric subjects occurred uncommonly (≥ 1/1000 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 NPLATE in 4 controlled and 5 uncontrolled clinical studies, 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 studies, NPLATE treatment was discontinued in 4 of the 271 patients because of bone marrow reticulin deposition. In 6 additional patients reticulin was observed upon bone marrow biopsy (see section 4.4).

Immunogenicity

Clinical trials in adult ITP patients examined antibodies to romiplostim. While 5,7 % and 3,2 % of the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 4) were positive for neutralising antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. All 4 subjects tested negative for neutralising antibodies to romiplostim at 4 months after the end of dosing. The incidence of pre-existing antibodies to romiplostim and TPO was 3,3 % (35/1046) and 3,0 %,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 neutralizing 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 neutralizing

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. 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.

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact Amgen South Africa (Pty) Ltd. on 011-100 5300for antibody testing.

*d) Paediatric population*

In the paediatric studies, 224 paediatric ITP subjects were treated with romiplostim. The overall safety profile was similar to that seen in adults.

The most common adverse reactions in paediatric ITP patients 1 year and older (≥ 5 % and greater than placebo) 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, urticarial 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.

Adverse reactions from post-marketing experience

The frequency category of the adverse reactions identified from spontaneous reporting that have not been reported in clinical trials cannot be estimated.

- Vascular disorders: Erythromelalgia.
- Hypersensitivity reactions including angioedema. Patients also experienced symptoms consistent with anaphylaxis.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

**4.9 Overdose**

No adverse effects were seen in rats given a single dose of 1000 µg/kg or in

monkeys after repeated administration of romiplostim at 500 µg/kg (100 or 50 times the maximum clinical dose of 10 µg/kg, respectively). In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue NPLATE and monitor platelet counts. Re-initiate treatment with NPLATE in accordance with dosing and administration recommendations (see section 4.2 and 4.4).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

A 8.2 Medicines acting on blood and haemopoietic system – Others

Mechanism of Action

Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*). Romiplostim is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the thrombopoietin (TPO) receptor (also known as cMpl) to increase platelet production.

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

Clinical efficacy and safety

Adults:

The safety and efficacy of romiplostim in adults were evaluated in two placebo-controlled, double-blind studies (Study 1 and Study 2) and an open-label single-arm study (Study 3), .

Study 1 and Study 2 were conducted 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 1 (20030212) evaluated patients who were nonsplenectomised 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 2 (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 randomized in a 2:1 ratio to receive a starting dose of romiplostim 1 µg/kg or placebo. Patients received single weekly SC 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 in the romiplostim-treated patients compared to the placebo treated patients. In these placebo-controlled studies, the most frequently used weekly dose during weeks 17-24 for splenectomised patients was between 2 - 7 µg/kg ($25^{th}$ - $75^{th}$ percentile respectively; median 3 µg/kg)

and for nonsplenectomised patients was between 1-3 µg/kg (25th - 75th percentile respectively; median 2 µg/kg). As shown in Table 6 treatment with romiplostim demonstrated significant improvements compared to placebo in both clinical studies for all efficacy endpoints.

Following discontinuation of romiplostim during Study 1 and Study 2, seven patients maintained platelet counts of ≥ 50 x $10^9$/l until week 36 and were not enrolled in the extension study.

**Table 6. Summary of Efficacy Results from Placebo-controlled Studies**

| | Study 1 Nonsplenectomised 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) | 7.5 | 3.5 | 7.9 | 0.5 | 7.8 | 2.5 |
| p-value | < 0,0001 | | < 0,0001 | | < 0,0001 | |
| No. (%) Patients Requiring Rescue Therapies[d] | 8 (20 %) | 13 (62 %) | 11 (26 %) | 12 (57 %) | 19 (23 %) | 25 (60 %) |

| | | | | | | |
|---|---|---|---|---|---|---|
| (95 % CI) | (8.8 %, 35 %) | (38 %, 82 %) | (14 %, 42 %) | (34 %, 78 %) | (14 %, 34 %) | (43 %, 74 %) |
| p-value | 0,0010 | | 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 medication 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 medications.

[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 medications.

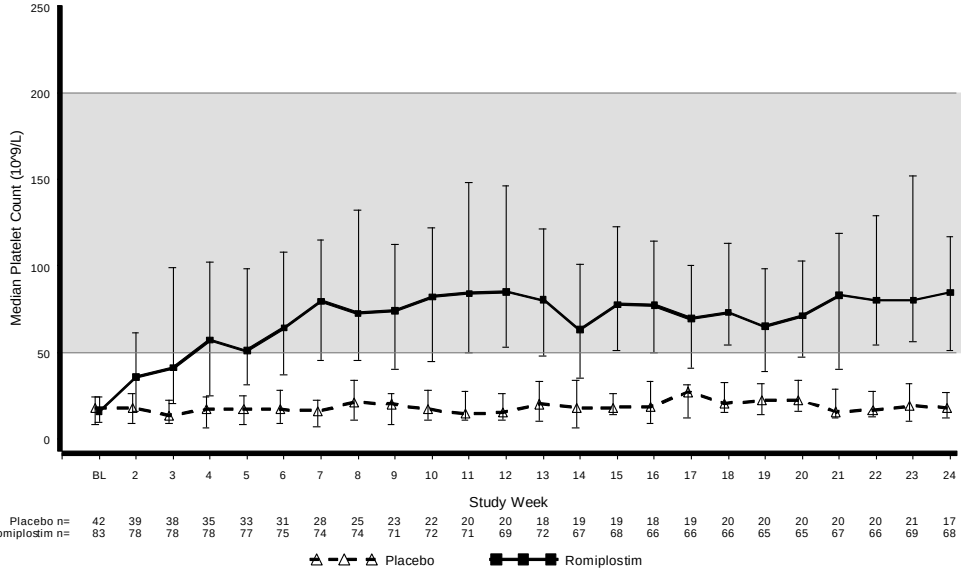
[d] Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medications were not considered for durable platelet response. Rescue therapies allowed in the study were IVIG, platelet transfusions, anti-D immunoglobulin, and corticosteroids.

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

In both Study 1 and Study 2, 30 % of patients treated with romiplostim achieved a platelet count above 50 x $10^9$/l by week 2, 54 % by week 4, and 50 % to 70 % of patients maintained platelet counts ≥ 50 x $10^9$/l for the remainder of the Phase 3 studies. In the placebo group, 0 % to 7 % of patients were able achieve a platelet count response during the 6 months of treatment.

Figure 1 shows the median weekly platelet counts over the 6 months of treatment in the Phase 3 studies.

**Figure 1. Median (Q1, Q3) Weekly Platelet Counts in Phase 3 Studies**




Full analysis set includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
Baseline platelet value (BL) = mean of platelet counts at Days -8, -2 and pre-dose Day 1.

Study 3 (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 had ITP duration < 3 months and 40 % 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 NPLATE 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 NPLATE dose was 3 µg/kg (25th 75th percentile: 2-4 µg/kg).

Of the 75 patients enrolled in Study 3, 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 maintained every platelet count ≥ 50 x $10^9$/l for at least 6 months in the absence of NPLATE 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).

Paediatrics:

The safety and efficacy of romiplostim in paediatric patients aged 1 year and older with ITP were evaluated in two double-blind, placebo-controlled studies (Study 4 and Study 5).

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.

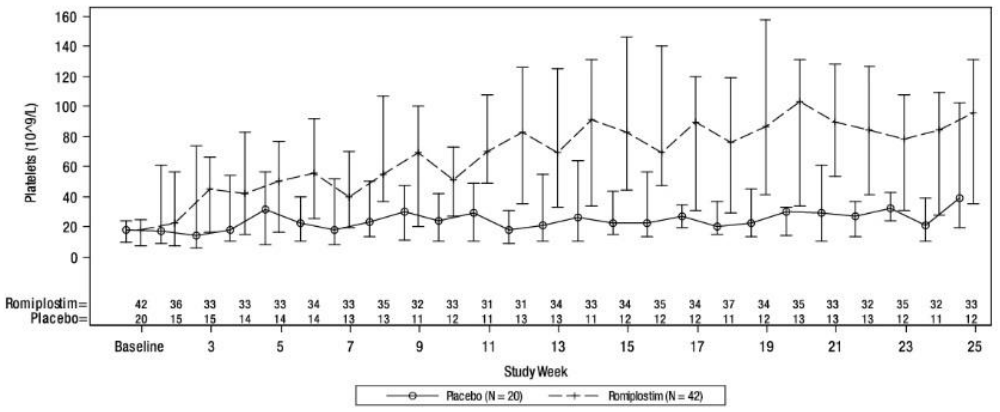
*Study 4 (20080279):*

Study 4 was a Phase 3 study with 24 weeks of romiplostim treatment. Patients refractory or relapsed after at least one prior ITP therapy with a platelet count ≤ 30 x $10^9$/l were stratified by age (into 1 of 3 age cohorts) and randomized in a 2:1 ratio to receive romiplostim (n = 42) or placebo (n = 20). Patients received single subcutaneous weekly injections for 24 weeks. The starting dose of romiplostim was 1 µg/kg weekly. The dose was adjusted over the 24-week

treatment period to maintain (50 to 200 x $10^9$/l) platelet counts. The most frequently used weekly dose was between 3 - 10 µg/kg and the maximum allowed dose on study was 10 µg/kg.

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 significantly greater proportion of patients in the romiplostim arm achieved the primary endpoint compared with subjects in the placebo arm (p = 0.0018). A total of 22 patients (52 %) had durable platelet response in the romiplostim arm compared with 2 patients (10 %) in the placebo arm: ≥ 1 to < 6 years 38 % vs 25 %; ≥ 6 to < 12 years 56 % vs 11 %; ≥ 12 to < 18 years 56 % vs 0.

**Figure 2. Median Plot of Platelet Count with Q1 and Q3 (Efficacy Analysis Set)**




Vertical lines represent the first and third quartiles around the median.
Platelet counts measured within 4 weeks following a rescue medication use or after splenectomy were excluded.

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The composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinically 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 (clinical grade ≥ 2) 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. The overall duration-adjusted rate per 100 subject-weeks was 8,1 in the romiplostim arm and 18,4 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 according to the pre-specified sequential testing scheme for multiplicity adjustment. In an ad hoc analysis, the duration-adjusted rate (per 100 subject-weeks) of these episodes was lower with romiplostim than placebo (8,1 vs 18,4; treatment difference -10,3, 95 % CI -14,7, -5,9).

*Study 5 (20060195):*

Study 5 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).

22 patients were randomized in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 µg/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 the 17 patients who received romiplostim, 15 achieved a platelet count of ≥ 50 x $10^9$/l for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88,2 %, 95 % CI: 63,6 %, 98,5 %). The same 15 subjects also achieved an increase in platelet count of ≥ 20 x $10^9$/l above baseline for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88.2 %, 95 % CI: 63,6 %, 98,5 %). None of the

patients treated with placebo achieved either endpoint.

Reduction in Permitted Concurrent ITP Medical Therapies

Adults:

In Study 1 and Study 2, patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the study (i.e., corticosteroids, danazol and/or azathioprine). Twenty-one nonsplenectomised and 18 splenectomised patients received on-study ITP medical treatments (primarily corticosteroids) at the start of the study. All 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. Seventy three percent of nonsplenectomised 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 (see section 4.5.1 Interference with Laboratory and Diagnostic Tests).

Table 7 describes the number of Phase 3 study patients who were able to reduce the dose by more than 25 % or discontinue baseline ITP therapies by week 25 (end of treatment), for Study S1 (212), Study S2 (105), and both studies combined:

**Table 7. Concurrent ITP Medical Therapies**

| | Study 1 Nonsplenectomised 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. of Patients receiving Baseline Concurrent ITP Medical Therapies | 11 | 10 | 12 | 6 | 23 | 16 |
| At Week 25, No. ( %) of Patients who: [a,b] | | | | | | |
| had > 25 % dose reduction[d] | 4 (36 %) | 2 (20 %) | 4 (33 %) | 1 (17 %) | 8/23 (35 %) | 3/16 (19 %) |
| Discontinued [c,e] | 4 (36 %) | 3 (30 %) | 8 (67 %) | 0 (0 %) | 12/23 (52 %) | 3/16 (19 %) |

*[a] Percentage was calculated based on number of patients with baseline concurrent ITP therapy.*

*[b] Patients counted in discontinuation were not counted again in reduction.*

*[c] If a patient withdrew from study early, the last record of the baseline concurrent ITP medicine was used.*

*[d] For multiple baseline concurrent ITP therapies, at least one therapy with > 25 % dose reduction was observed without an increase in other ITP therapies.*

*[e] For multiple baseline concurrent ITP therapies, all therapies must have been discontinued.*

Paediatrics:

In the integrated analysis, the subject prevalence of concurrent ITP therapy use was 39,7 % (89 of 224 subjects) at any time during treatment, and there was a trend towards a reduction in concomitant medication use over time.

Use of Rescue Therapies

Adults:

Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for haemorrhage. The total incidence of rescue therapy use

was considerably higher for patients treated with placebo than with romiplostim in both splenectomised and nonsplenectomised patients (see Table 6, Summary of Efficacy Results from Placebo-controlled Studies).

Paediatrics:

The subject incidence of rescue medication use was 32.6 % (73 of 224 subjects) at any time during treatment, and there was a trend towards a reduction in rescue medication use over time.

Use of Romiplostim in Nonsplenectomised ITP Patients compared with SOC

Adults:

Study 6 (20060131) was an open-label, randomized, 52-week trial in subjects who received romiplostim or medical 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. Medical SOC treatments were selected and prescribed by the investigator according to standard institutional practices or therapeutic guidelines. This study evaluated nonsplenectomised patients with ITP and platelet counts < 50 x $10^9$/l. Romiplostim was administered by subcutaneous (SC) injection once weekly starting at a dose of 3 µg/kg, and adjusted throughout the study within a range of 1 - 10 µg/kg in order to maintain platelet counts between 50 and 200 x $10^9$/l.

The efficacy of romiplostim was found to be significantly greater (i.e., lower rates of splenectomy and treatment failure) than that of medical SOC. The overall subject incidence 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. The p-value for the treatment difference between groups is < 0.0001, with an odds ratio (romiplostim vs SOC) of 0.17 (95 % CI: 0,08, 0,35), indicating that the odds of undergoing a splenectomy is statistically significantly lower in the

romiplostim group than the SOC group.

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. The p-value for the treatment difference between groups is 0,0005, with an odds ratio (romiplostim vs SOC) of 0,31 (95 % CI: 0,15, 0,61), indicating that the odds of experiencing treatment failure is statistically significantly lower in the romiplostim group than the SOC group.

Of the 157 subjects randomized to the romiplostim group in Study 6, the total median exposure to romiplostim for the 154 subjects that received romiplostim was 52,0 weeks and ranged from 2 to 53 weeks. The most frequently used weekly dose was between 3-5 µg/kg ($25^{th}$ - $75^{th}$ percentile respectively; median 3 µg/kg).

Open Label Long-term Efficacy

Adults:

Patients who had completed a prior romiplostim study (including Study 1 and Study 2) were allowed to enrol in a long-term open-label extension study (Study 7, 20030213). Romiplostim was administered by SC injection once weekly starting either at the same dose being received at the end of treatment in the previous study or at a dose of 1 µg/kg (for subjects who had received placebo in a previous study). Patients entering the extension study that had been off study drug for > 24 weeks started at a dose of 1 µg/kg. Among 291 adult patients who subsequently received romiplostim in the extension study, platelet counts were increased and sustained regardless of whether they had received romiplostim or placebo in the prior placebo-controlled studies. The majority of patients reached a median platelet count of 50 x $10^9$/l after receiving one to three doses of romiplostim, and these platelet counts were

maintained throughout the remainder of the study with a median duration of romiplostim treatment of 78 weeks and a maximum duration of 277 weeks.

After the initial dose adjustment period, the majority of adult subjects were able to maintain their dose within 2 µg/kg, suggesting maintenance of clinical effect over time in the absence of significant romiplostim dosage increases. The overall subject incidence of rescue medication use in adult subjects was 33,3 %. Approximately 13 % (37/291) of adult subjects were receiving concurrent ITP therapy at the time of study entry. Twenty (54,1 %) of these subjects had discontinued concurrent ITP therapy by the end of the study. Of the 38 subjects who had bone marrow biopsies, no evidence of type I collagen was observed, however, trichrome staining for type I collagen was inconsistently performed.

Paediatrics:

Study 8 (20101221) was a Phase 3, 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 or were ineligible for other ITP therapies. Romiplostim was administered weekly by subcutaneous injection starting at a dose of 1 µg/kg with weekly increments to a maximum dose of 10 µg/kg to reach a target platelet count between 50 x $10^9$/l and 200 x $10^9$/l

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.

Further, an extension of the Phase 1/2 study (Study 5) was conducted in 20 paediatric patients (Study 7) [213 (Open enrolment for Study 5)], who were administered romiplostim once weekly. Dosing started either at the same dose being received at the end of treatment in the previous study or at a dose of 1 µg/kg (for subjects who had received placebo in a previous study).

Platelet response (≥ 50 x $10^9$/l at any time during the study) was achieved in 100,0 % of the paediatric subjects (95 % CI: 83,2 %, 100,0 %). A platelet count of ≥ 100 x $10^9$/l was reached in 90,0 % of paediatric subjects and a peak platelet count of ≥ 150 x $10^9$/l was reached in 85,0 % of paediatric subjects. The overall subject incidence of rescue medication use in the paediatric population was 20,0 % (4 subjects).

Open Label Study Evaluating Changes in Bone Marrow Reticulin and Collagen

Adults:

An open-label trial prospectively evaluated bone marrows for reticulin formation and collagen fibrosis in adult patients with ITP receiving romiplostim treatment. The modified Bauermeister grading scale was used for both assessments. Patients were administered romiplostim by SC injection once weekly for up to 3 years. Based on cohort assignment at the time of study enrolment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1), year 2 (cohort 2) or year 3 (cohort 3) in comparison to the baseline bone marrow at the start of the study. In total, 1,5 % (2 of 132) of patients with an evaluable bone marrow trichrome stain result developed collagen. There was no detectable collagen in the one patient who underwent repeat testing 12 weeks after discontinuation of romiplostim. Progression of reticulin fibre formation greater than or equal to 2 grades or more change or an increase to Grade 4 collagen was reported in 6,9 % (9/131) of patients.

Paediatrics:

An open-label trial (Study 8, 20101221) evaluated bone marrows for reticulin and collagen formation in paediatric patients with ITP receiving romiplostim treatment. The modified Bauermeister grading scale was used for both assessments. Patients were administered romiplostim by SC injection once weekly for up to 3 years. 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. 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 µg/kg romiplostim, maximum romiplostim serum levels in ITP patients were obtained after 7to 50 hours (median 14 hours). The serum concentrations varied among patients and did not correlate with the dose administered.

Romiplostim serum levels appear inversely related to platelet counts.

**Distribution:**

The volume of distribution of romiplostim following intravenous administration of romiplostim decreased nonlinearly from 122; 78,8; to 48,2 ml/kg for intravenous

doses of 0,3; 1,0 and 10 µg/kg, respectively in healthy subjects. This non-linear decrease in volume of distribution is in line with the (megakaryocyte and platelet) target-mediated binding of romiplostim, which may be saturated at the higher doses applied.

**Elimination:**

Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3,5 days). The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and *vice versa*. In another ITP clinical study, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 µg/kg).

Special patient 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 in21 paediatric subjects with ITP. In Study S5, romiplostim concentrations were available from 17 subjects at doses ranging from 1 to 10 µg/kg. In Study S6, intensive romiplostim concentrations were available from 4 subjects (2 at 7 µg/kg and 2 at 9 µg/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/Nonclinical toxicology

Multiple dose romiplostim toxicology studies were conducted in rats for 4 weeks (0 to 100 µg/kg/3 times per week) and in monkeys for up to 6 months (0 to 5000 µg/kg/ up to once weekly). 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.

Increased reticulin described as myelofibrosis has been observed in the bone marrow of rats. In these studies, myelofibrosis was not observed in animals after a 4-week post-treatment recovery period, indicating reversibility.

No adverse effects were seen in monkeys given a single dose of 5000 µg/kg (500 times the recommended maximum clinical dose of 10 µg/kg).

**Carcinogenesis:**

The carcinogenic potential of romiplostim has not been evaluated.

**Mutagenesis:**

The mutagenic potential of romiplostim has not been evaluated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Contains sugar (sucrose and mannitol).

L-histidine

Dilute 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**

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 (between 2 °C and 8 °C) when the diluted product was held in the original vial.

From a microbiological point of view, the diluted 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 than4 hours at 25 °C in disposable syringes, or 4 hours in a refrigerator (between 2 °C and 8 °C) in the original vials, protected from light.

**6.4 Special precautions for storage**

Store in a refrigerator (between 2 °C and 8 °C).

Do not freeze.

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

May be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25 ºC).

**6.5 Nature and contents of container**

5 ml clear glass vial (type 1) with a grey stopper (chlorobutyl rubber), aluminium seal and a red (250 µg) or blue (500 µg) flip-off cap (polypropylene).

Carton containing 1 or 4 vials of romiplostim.

Not all pack sizes may be marketed.

**6.6 Special Precautions for disposal and other handling**

Romiplostim is supplied in two vial presentations containing sufficient product to produce a deliverable dose of 250 µg or 500 µg when reconstituted as instructed.

Reconstitution

The 250 µg single-use vial to be reconstituted with 0,72 ml of Sterile Water for Injection, yielding a deliverable 500 µg/ml concentration (total extractable dose per vial is 250 µg in 0,5 ml). An additional overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered.(see table 5: Vial content table below).

The 500 µg single-use vial to be reconstituted with 1,20 ml Sterile Water for Injection, yielding a 500 µg/ml concentration (total extractable dose per vial is 500 µg in 1,0 ml). An additional overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered (see table 5: Vial content table below).

**Table 5: Vial Content**

| Single-use vials of romiplostim | | Sterile Water for Injection | | Deliverable product/volume |
|---|---|---|---|---|
| • 250 µg | add | 0,72 ml | = | 250 µg /0,5 ml |
| • 500 µg | add | 1,20 ml | = | 500 µg /1,0 ml |

Sterile Water for Injection only should be used when reconstituting the medicinal product.

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

During reconstitution, the vial contents may be gently swirled and inverted. Avoid

excess or vigorous agitation: DO NOT SHAKE. Generally, dissolution of romiplostim takes less than 2 minutes. The reconstituted romiplostim solution should be clear and colourless. Visually inspect the reconstituted solution for particulate matter and/or discoloration. Do not administer romiplostim if particulate matter and/or discoloration is observed. Reconstituted product should be administered within 24 hours, as it does not contain a preservative. The reconstituted product can remain at room temperature 25 °C or be refrigerated at 2 to 8 °C for up to 24 hours prior to administration. The reconstituted product must be protected from light.

Reconstituted product may be held in a syringe for a maximum of 4 hours, though it is recommended that the reconstituted product be used immediately upon reconstitution.

Product sterility, post-reconstitution, depends on aseptic technique and the environment in which the dose was prepared. During the time the reconstituted romiplostim is stored in the syringe, the temperature should not exceed 25 °C and must be protected from light.

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.

Vial content:

| NPLATE single-use vial | Total vial content of romiplostim | | Volume of Sterile Water for Injection | | Deliverable product and volume | Final concentration |
|---|---|---|---|---|---|---|
| 250 µg | 375 µg | + | 0,72 ml | = | 250 µg in 0,5 ml | 500 µg/ml |

| | | | | | | |
|---|---|---|---|---|---|---|
| 500 µg | 625 µg | + | 1,20 ml | = | 500 µg in 1,0 ml | 500 µg/ml |

Dilution (Required when the calculated individual patient dose is less than 23 µg)

Initial reconstitution of romiplostim with designated volumes of Sterile Water for Injection results in a concentration of 500 µg/ml in all vial sizes. If the calculated individual patient dose is less than 23 µg (see section 4.2),
then an additional dilution step to 125 µg/ml with preservative-free, sterile, 0,9 % sodium chloride (USP or equivalent) is required to ensure accurate volume (see table 6 below).

Table 6: 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 |
|---|---|---|
| 250 µg | 2,25 ml | 125 µg/ml |
| 500 µg | 3,75 ml | 125 µg/ml |

Preservative-free sterile 0,9 % sodium chloride 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.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.

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35 Ballyclare Drive

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South Africa

2021

## 8. REGISTRATION NUMBER(S)

NPLATE 250 µg: 45/8.2/0175

NPLATE 500 µg: 45/8.2/0176

## 9. DATE OF FIRST AUTHORIZATION

07 December 2012

## 10. DATE OF REVISION OF TEXT

04 March 2021