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# Romiplate® 250µg
**powder for solution for Injection**

## 1. NAME OF THE MEDICINAL PRODUCT

Romiplate® 250 µg, powder for solution for Injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

*Chronic immune (idiopathic) thrombocytopenic purpura (ITP)*

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

Romiplate® may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

*Aplastic anaemia*

Romiplate® is indicated for adults with moderate to severe aplastic anaemia refractory to conventional therapies.

### 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

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

*Initial dose*

*Chronic immune (idiopathic) thrombocytopenic purpura (ITP)*

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

*Aplastic anaemia*

Usually administer an initial dose of 10 µg/kg subcutaneously as romiplostim (genetical recombination) for adults. After initiation of treatment, the dose may be adjusted based on the patient's condition, and administer once weekly. The maximum weekly dose is 20 µg/kg.

*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**

| | |
|---|---|
| Initial or subsequent once weekly dose: | Weight* in kg x Dose in µg/kg = Individual patient dose in µg |
| Volume to administer: | Dose in µg x $\frac{1 \text{ mL}}{500 \text{ µg}}$ = Amount to inject in mL |
| Example: | 75 kg patient is initiated at 1 µg/kg of romiplostim.<br>The individual patient dose =<br><br>75 kg x 1 µg/kg = 75 µg<br><br>The corresponding amount of Romiplate® solution to inject<br>= 75 µg x $\frac{1 \text{ mL}}{500 \text{ µg}}$ = 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 µg/kg increments (see Table below). | |

*Dose adjustments*

A subject's actual body weight at initiation of therapy should be used to calculate dose.

*Chronic immune (idiopathic) thrombocytopenic purpura (ITP)*

The once weekly dose of romiplostim should be increased by increments of 1 µg/kg until the patient achieves a platelet count ≥ 50 x $10^9$/L. Platelet counts should be assessed weekly until a stable platelet count (≥ 50 x $10^9$/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed 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 µg/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 µg/kg |
| > 150 for two consecutive weeks | Decrease once weekly dose by 1 µg/kg |
| > 250 | Do not administer, continue to assess the platelet count weekly<br><br>After the platelet count has fallen to < 150 x $10^9$/L, resume dosing with once weekly dose reduced by 1 µg/kg |

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

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).

*Aplastic anaemia*

Blood count should be measured weekly at the initial treatment phase and during the dose adjustment phase. Even if the dose has been maintained, it should be measured about once in 4 weeks.

Generally, the dose should be adjusted with increments of 5 µg/kg. Do not exceed a maximum once weekly dose of 20 µg/kg.

Dose increase should be considered in cases where platelet count has not risen (e.g. increase by ≥ 20 × $10^9$/L from baseline or increase to ≥ 10 × $10^9$/L and ≥ 100% increase from baseline with blood transfusion independence) though the same dose has been administered for 4 consecutive weeks.

Use romiplostim at the lowest dose required for treatment in accordance with the following table:

| Platelet count (x $10^9$/L) | Adjustment rule |
|---|---|
| 200 - 400 | Reduce the dose. |
| > 400 | Suspend treatment. Once the platelet count has fallen to 200 × $10^9$/L after suspension of treatment, resume romiplostim lower dose compared to the dose prior to suspension. If the dose before suspension of treatment was 5 µg/kg or lower, and if the platelet count has fallen to 50 × $10^9$/L, treatment may be resumed at the same dose as before suspension of treatment. |

Reduce the dose in case where 3 blood cell lineage improvement is observed (e.g. platelet count above $50 \times 10^9$/L with blood transfusion independence, hemoglobin above 10 g/dL with blood transfusion independence, and neutrophil count above $1 \times 10^9$/L) for at least 8 consecutive weeks. If the improvement in 3 blood lineages has been maintained with the reduced dose for 4 weeks, further reduce the dose and consider subsequent dose reduction every 4 weeks (In the case of 5 μg/kg or lower, consider suspension of treatment). If the condition has worsened in any of the 3 blood cell lineages, consider a dose increase (if the treatment has been suspended, it may be resumed at the previous dose).

*Treatment discontinuation*

*Chronic immune (idiopathic) thrombocytopenic purpura (ITP)*

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

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

*Aplastic anaemia*

Appropriate measures such as discontinuing romiplostim should be taken in cases where none of the 3 blood lineages has improved even though the maximum weekly dose of 20 μg/kg has been administered for 8 consecutive weeks.

*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*

Romiplate® is not recommended for use in children below age 18 due to insufficient data on safety or efficacy. No recommendation on a posology can be made in 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. Romiplate® should be used with caution in these populations.

Method of administration

For subcutaneous use.

After reconstitution of the powder, Romiplate® solution for injection is administered subcutaneously. The injection volume may be very small. Caution should be used during preparation of Romiplate® 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 Romiplate® is withdrawn from the vial for subcutaneous administration – a syringe with graduations of 0.01 mL should be used.

For instructions on reconstitution of Romiplate® before administration, see section 6.6.

Administration Precautions

Caution should be used during preparation of Romiplate® 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 Romiplate® is withdrawn from the vial for subcutaneous administration (see sections 4.4 for Special Warnings and Precautions for Use and 4.9 for Overdose).

## 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

The following special warnings and precautions have been actually observed or are potential class effects based on the pharmacological mechanism of action of thrombopoietin (TPO) receptor stimulators.

Reoccurrence of thrombocytopenia and bleeding after cessation of treatment

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with romiplostim. There is an increased risk of bleeding if romiplostim treatment is discontinued in the presence of anticoagulants or anti-platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of treatment with romiplostim. It is recommended that, if treatment with romiplostim is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

Increased bone marrow reticulin

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

release cytokines. Increased reticulin may be suggested by morphological changes in the peripheral blood cells and can be detected through bone marrow biopsy. Therefore, examinations for cellular morphological abnormalities using peripheral blood smear and complete blood count (CBC) prior to and during treatment with romiplostim are recommended. See Section 4.8 for information on the increases of reticulin observed in romiplostim clinical trials.

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

Thrombotic/thromboembolic complications

Platelet counts above the normal range present a risk for thrombotic/thromboembolic complications. The incidence of thrombotic/thromboembolic events observed in clinical trials was 6.0% with romiplostim and 3.6% with placebo. Caution should be used when administering romiplostim to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity, and smoking.

Cases of thromboembolic events (TEEs), including portal vein thrombosis, have been reported in patients with chronic liver disease receiving romiplostim. Romiplostim should be used with caution in these populations. Dose adjustment guidelines should be followed (see section 4.2)

Medication errors

Medication errors including overdose and underdose have been reported in patients receiving Romiplate®, dose calculation and dose adjustment guidelines should be followed.

Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue Romiplate® and monitor platelet counts. Reinitiate treatment with Romiplate® 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 Romiplate® (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, particularly in patients over 60 years of age, 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 blast cell increases 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 use for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.

Aplastic anaemia refractory to conventional therapy

Some patients with aplastic anaemia are known to progress to MDS or acute myeloid leukaemia (AML) during follow-up. In international clinical studies, some patients with aplastic anaemia refractory to conventional therapy were found to have chromosome abnormalities after administration of Romiplate®, although the causality was unclear.

During treatment with Romiplate®, a complete blood count including a differential leukocyte count and peripheral blood smear should be tested regularly in order to assess immature cells and morphological abnormalities, as well as cytopenia. If such abnormalities are found, consider a bone marrow test (including a chromosomal evaluation) to determine whether Romiplate® treatment should be continued.

Loss of response to romiplostim

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

Effects of romiplostim on red and white blood cells

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

Laboratory monitoring

Monitor CBCs, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of Romiplate® therapy. Prior to the initiation of Romiplate®, examine the peripheral blood differential to establish the baseline extent of red and white blood cell abnormalities. Obtain CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of Romiplate® therapy and then

monthly following establishment of a stable Romiplate® dose. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of Romiplate®.

## 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

Romiplate® 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 events 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 Romiplate® 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 | Gastroenteritis<br>Sinusitis***<br>Bronchitis*** | 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>Thrombocythaemia<br>Platelet count increased<br>Platelet count abnormal |
| Immune system disorder | Hypersensitivity** | Angioedema | |
| Metabolism and nutrition disorders | | | Alcohol intolerance<br>Anorexia<br>Decreased appetite<br>Dehydration<br>Gout |
| Psychiatric disorders | | Insomnia | Depression<br>Abnormal dreams |

| | | | |
|---|---|---|---|
| Nervous system disorders | Headache | Dizziness<br>Migraine<br>Paraesthesia | 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 disorders | | | Vertigo |
| 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 | | Pulmonary embolism* | Cough<br>Rhinorrhoea<br>Dry throat<br>Dyspnoea<br>Nasal congestion<br>Painful respiration |
| Gastrointestinal disorders | | Nausea<br>Diarrhoea<br>Abdominal pain<br>Constipation<br>Dyspepsia | 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>Rash papular<br>Rash pruritic<br>Skin nodule<br>Skin odour abnormal<br>Urticaria |
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia<br>Muscle spasms<br>Pain in extremity<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>Oedema peripheral<br>Influenza like illness<br>Pain<br>Asthenia<br>Pyrexia<br>Chills<br>Injection site reaction | Injection site haemorrhage<br>Chest pain<br>Irritability<br>Malaise<br>Face oedema<br>Feeling hot<br>Feeling jittery |
| Investigations | | | Blood pressure increased<br>Blood lactate dehydrogenase increased<br>Body temperature increased<br>Weight decreased<br>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 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 Romiplate® 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)).

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 Romiplate® 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)).

*Thrombocytosis*

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

*Thrombocytopenia after cessation of treatment*

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

*Progression of existing Myelodysplastic Syndromes (MDS)*

In a randomized placebo-controlled trial in MDS adult subjects 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).

*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.

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact the local product registration holder or Medical Representatives for antibody testing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system and to the local product registration holder.

Adverse reactions from spontaneous reporting:

The frequency category of the adverse reactions identified from spontaneous reporting that have not been reported in clinical trials cannot be estimated (Frequency: not known). The adverse reactions identified from spontaneous reporting include:

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

## 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 Romiplate® and monitor platelet counts. Reinitiate treatment with Romiplate® in accordance with dosing and administration recommendations (see section 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 thrombopoietin (TPO) receptor (also known as cMpl) to increase platelet production. The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing 2 TPO receptor-binding domains.

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

Clinical efficacy and safety

The safety and efficacy of romiplostim have been evaluated for up to 3 years of continuous treatment. In clinical trials, treatment with romiplostim resulted in dose-dependent increases in platelet count. Time to reach the maximum effect on platelet count is approximately 10-14 days, and is independent of the dose. After a single subcutaneous dose of 1 to 10 μg/kg romiplostim in ITP patients, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 weeks period and the response was variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 μg/kg of romiplostim were within the range of 50 to 450 x $10^9$/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 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 approximately 8 years (range 0.6 to 44.8) at the time of study entry. In addition to a splenectomy, patients had a median of 6 (range, 3 to 10) treatments for ITP prior to study entry. Prior treatments included corticosteroids (98% of all patients), immunoglobulins (97%), rituximab (71%), danazol (37%), cytotoxic therapies (68%), and azathioprine (24%). Patients had a median platelet

count of 14 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 μg/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 μg/kg and for non-splenectomised patients was 2 μg/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 μg/kg during the last 8 weeks of treatment.

*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 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 Romiplate® 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)).

Clinical data in patients with Aplastic Anaemia refractory to conventional therapy

*Global phase II/III studies*

In 31 adult patients, consisting of 24 Japanese and 7 South Korean patients, with aplastic anaemia who were refractory to immunosuppressive therapy including anti-thymocyte immunoglobulin or refractory to cyclosporine and not indicated for anti-thymocyte immunoglobulin, romiplostim was administered at an initial dose of 10 µg/kg once weekly and the dose was adjusted within a range of 5 to 20 µg/kg based on blood count. The haematological response rate at Week 27 was 83.9%, 95% CI = (66.3, 94.5). A haematological response rate is defined as the rate of patients with improvement in blood count at least 1 blood cell lineage.

The incidence of adverse reactions was 54.8% (17/31 patients). The most frequently observed adverse reactions in Japanese patients were headache and muscle spasms in 16.7% each (4/24 patients), and alanine aminotransferase increased, fibrin D dimer increased, malaise, and pain in an extremity in 8.3% each (2/24 patients). In Korean patients, only platelet count increased was observed in 14.3% (1/7 subjects).

*Criteria for haematological response*

| | |
|---|---|
| Platelet count | ≥ 20 x $10^9$/L increase, ≥ 10 x $10^9$/L equivalent to ≥ 100% increase from baseline, or platelet transfusion independence for 8 consecutive weeks |
| Haemoglobin level | ≥ 1.5 g/dL increase without red blood cell transfusion in patients with less than 9 g/dL or decrease in volume of red blood cell transfusion (at least 800 mL decrease in total transfusion volume in 8 consecutive weeks) |
| Neutrophil count | ≥ 100% increase in neutrophil count in patients with less than 0.5 x $10^9$/L or ≥ 0.5 x $10^9$/L increase in patients with less than 1 x $10^9$/L |

## 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.

*Chronic immune (idiopathic) thrombocytopenic purpura (ITP)*

Absorption

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

Distribution

The volume of distribution of romiplostim following intravenous administration of romiplostim decreased nonlinearly from 122, 78.8, to 48.2 mL/kg for intravenous doses of

0.3, 1.0 and 10 µg/kg, respectively in healthy subjects. This non-linear decrease in volume of distribution is in line with the (megakaryocyte and platelet) target-mediated binding of romiplostim, which may be saturated at the higher doses applied.

Elimination

Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3.5 days).

The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result for a given dose, patients with high platelet counts are associated with low serum concentrations and *vice versa*. In another ITP clinical trial, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 µg/kg).

*Aplastic anaemia*

For 13 Japanese and Korean adult patients with aplastic anaemia, who had inadequate response to immunosuppressive therapy and had been administered with Romiplate® at a dose of 10 µg/kg once a week by subcutaneous injection for 4 weeks, the serum pharmacokinetics parameters of Romiplate® are shown below.

The serum pharmacokinetic parameters of romiplostim at Week 4 in patients with aplastic anaemia who did not respond well to immunosuppressive therapy after subcutaneous injection of 10µg/kg once a week for 4 consecutive weeks.

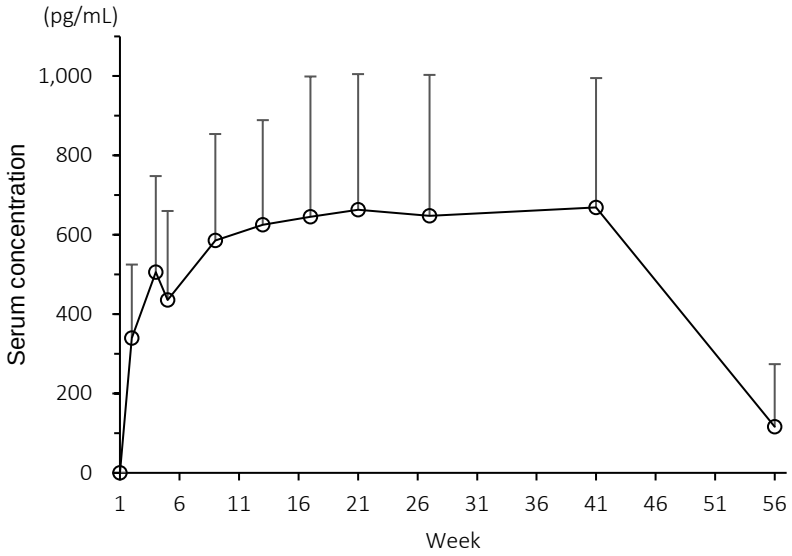
| Dose (µg/kg) | Number of subjects | $AUC_{0\sim168h}$ (pg・h/mL) | $C_{max}$ (pg/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| 10 | 13 | 267000 ±150000 | 5040 ±2800 | 13.96 ±11.42 | 90.0 ±35.6 |

*The data is presented as "mean ± standard deviation"; 13 subjects include "8 subjects in Japan and 5 subjects in Korea".*

Regarding 31 Japanese and Korean adult patients with aplastic anaemia who had inadequate response to immunosuppressive therapy, the Serum $C_{trough}$-time curve of Romiplostim for once-weekly subcutaneous administration at 10 µg/kg from Week 1 to 4 and once-weekly adjustment at 5 µg/kg (acceptable dose adjustment range: 5-20 µg/kg) based on platelet response and blood count from Week 5 to 52 are as shown below.

| Distribution of Romiplate® dosage (µg/kg) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1-4 | 5 | 9 | 13 | 17 | 21 | 24 | 27 | 31 | 35 | 41 |
| 10.0 | 14.0 | 16.1 | 16.9 | 16.9 | 16.7 | 16.2 | 15.9 | 15.9 | 15.9 | 15.2 |

The serum $C_{trough}$-time curve of Romiplostim (mean + standard deviation) from Week 1 to 56 for patients with aplastic anaemia who have inadequate response to immunosuppressive therapy.




| Week | 1 | 2 | 4 | 5 | 9 | 13 | 17 | 21 | 27 | 41 | 56* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of subjects | 30 | 13 | 31 | 13 | 29 | 30 | 29 | 29 | 28 | 27 | 31 |

**For subjects who discontinued treatment, serum romiplostim concentration measured 4 weeks after the last dose was used as the Week 56 data.*

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.

**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

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

### 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.
May be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C).
For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

5 mL vial with a stopper and a sealing cap
Carton containing 1 vial of 250 µg of romiplostim.

### 6.6 Special precautions for disposal and other handling

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

Romiplate® 250µg, Injection should be reconstituted with 0.72 mL sterile water for injections, yielding a deliverable volume of 0.5 mL. An additional overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered. Do not administer more than one dose from a vial.

From a biological 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.

Sterile water for injections only should be used when reconstituting the medicinal products. 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 Romiplate® 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 product or waste material should be disposed of in accordance with local requirements.
Product Owner:
Kyowa Kirin Co., Ltd.
1-9-2, Otemachi, Chiyoda-ku
Tokyo, Japan

Product Registrant:
Kyowa Kirin Asia Pacific Pte. Ltd.
80 Robinson Road, #22-01
Singapore 068898

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