ROMY

Romiplostim Powder and Solvent for Solution for Injection, 250 mcg/0.5 mL and 500 mcg/1.0 mL in vial

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For Use of Registered Hematologist /Oncologist Only

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1. NAME OF THE MEDICINAL PRODUCT

Romiplostim powder and solvent for solution for injection, 250 mcg/0.5 mL and 500 mcg/1.0 mL in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Romiplostim 250 micrograms powder and solvent for solution for injection

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

Romiplostim 500 micrograms powder and solvent for solution for injection

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

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

For the full list of excipients, see section List of excipients.

3. PHARMACEUTICAL FORM

Powder and solvent for reconstitution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Romiplostim is indicated for chronic immune thrombocytopenic purpura (ITP) patients one year of age and older who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

4.2 Posology and Method of Administration

During a phase III clinical study in patients with chronic refractory ITP, Intas Romiplostim was initiated and administered as 1 mcg/kg subcutaneous injection every week for 8 weeks. Dose was adjusted based on results of platelet counts to a maximum of 5 mcg/kg.

Information provided below is based on innovator data.

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

Posology

Romiplostim should be administered once weekly as a subcutaneous injection.

Initial dose

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

Dose calculation

The volume of romiplostim, to be administered, is calculated based on body weight, dose required, and concentration of product as shown in below table,

Table 1: Guidelines for Calculating Individual Patient Dose and Volume of Romiplostim to Administer

Initial patient dose (mcg):	Individual patient dose (mcg) = Weight (Kg) x Dose in mcg/kg Actual body weight at initiation of treatment should always be used when calculating initial dose. • In adults, future dose adjustments are based on changes in platelet counts only. • In pediatric patients, future dose adjustments are based on changes in platelet counts and **changes in body weight**. Reassessment of body weight is recommended every 12 weeks
Volume to administer:	
If individual patient dose is ≥23 mcg	Reconstitute lyophilised product as described in section “Special precautions for disposal and other handling”. The resulting concentration is 500 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg) x 1 mL/500 mcg (Round volume to the nearest hundredth mL)
If individual patient dose is <23 mcg	Dilution is required to ensure accurate dosing. Reconstitute lyophilised product and then dilute the product as described in section “Special precautions for disposal and other handling”. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg) x 1 mL/125 mcg (Round volume to the nearest hundredth mL)
Examples:	For individual patient dose ≥23 mcg 75 kg patient is initiated at 1 mcg/kg of Romiplostim. The individual patient dose = 75 kg x 1 mcg/kg = 75 mcg Volume to administer (mL) = 75 mcg x 1 mL/500 mcg = 0.15 mL For individual patient dose <23 mcg 10 kg patient is initiated at 1 mcg/kg of romiplostim. The individual patient dose = 10 kg x 1 mcg/kg = 10 mcg Because the dose is <23 mcg, dilution is required to ensure accurate dosing. Reconstitute lyophilised product and then dilute the product as described in “Special precautions for disposal and other handling”. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = 10 mcg x 1 mL/125 mcg = 0.08 mL

Dose adjustments

A subject’s actual body weight at initiation of therapy should be used to calculate dose. The once weekly dose of romiplostim should be increased by increments of 1 mcg/kg until the patient achieves a platelet count ≥50 x 10^9/L. Platelet counts should be assessed weekly until a stable platelet count (≥50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed monthly thereafter and appropriate dose adjustments should be made as per the dose adjustment table (Table 2) in order to maintain platelet counts within the recommended range. See Table 2 below for dose adjustment and monitoring. A maximum once weekly dose of 10 mcg/kg should not be exceeded.

Table 2: Dose Adjustment Guidance Based on Platelet Count

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

Due to the interindividual variability in platelet response, in some patient’s 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 judgment.

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.

Treatment discontinuation

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

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

Elderly patients (≥65 years)

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

Pediatric population

The safety and efficacy of romiplostim in children under the age of one year has not been established.

Patients with hepatic impairment

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

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

Patients with renal impairment

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

Method of administration

For subcutaneous use.

After reconstitution of the powder, romiplostim solution for injection is administered subcutaneously. The injection volume may be very small. Caution should be used during preparation of romiplostim in calculating the dose and reconstitution with the correct volume of sterile water for injection. If the calculated individual patient dose if less than 23 mg, dilution with preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection is required to ensure accurate dosing (see section “Special precautions for disposal and other handling”). Special care should be taken to ensure that the appropriate volume of romiplostim is withdrawn from the vial for subcutaneous administration – a syringe with graduations of 0.01 mL should be used.

Self-administration of romiplostim is not allowed for pediatric patients.

For instructions on reconstitution and administration of the medicinal product, see section “Special Precautions for Disposal and Other Handling”.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “List of Excipients” or to *E. coli* derived proteins.

4.4 Special warnings and precautions for use

Information provided below is based on innovator data.

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 “Undesirable effects” section 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 immobilization, 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.

Medication errors

Medication errors including overdose and underdose have been reported in patients receiving romiplostim, dose calculation and dose adjustment guidelines should be followed. In some pediatric patients, accurate dosing relies on an additional dilution step after reconstitution which may increase the risk for medication errors.

Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue romiplostim and monitor platelet counts. Reinitiate treatment with romiplostim 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 romiplostim.

Progression of existing Myelodysplastic Syndromes (MDS)

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

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

In clinical studies of treatment with romiplostim in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported. In a randomized placebo-controlled trial in MDS subjects, treatment with romiplostim was prematurely stopped due to a numerical excess of disease progression to AML and an increase in circulating blasts greater than 10% in patients receiving romiplostim. Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML compared to lower risk MDS.

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

Loss of response to romiplostim

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

Effects of romiplostim on red and white blood cells

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Information provided below is based on innovator data.

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.

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

4.6 Fertility, Pregnancy and Lactation

Information provided below is based on innovator data.

Fertility

There is no data available on fertility.

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.

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.

4.7 Effects on Ability to Drive and Use Machines

Information provided below is based on innovator data.

Romiplostim 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

Information provided below is based on the studies conducted with Intas Romiplostim.

In a prospective, open-label, multicentric, phase III study, adult patients with chronic refractory ITP were randomized to receive weekly SC injection of 1 mcg/kg Romiplostim (manufactured by Intas Pharmaceuticals Limited) for 8 weeks. Dose was increased based on platelet response as per investigators assessment. Total 50 male or female patients aged 18-65 years (both inclusive) with confirmed diagnosis of chronic refractory ITP at least 12 months before enrolment and who received at least 1 prior treatment for ITP were included in study. The dose was increased by 1 mcg/kg to 5 mcg/kg if platelet count was <50000/µL. The dose was reduced by 1 mcg/kg if platelet count was >200000/µL for 2 consecutive weeks. The patient was not dosed in case platelet count was >400000/µL. Patient was assessed for the platelet count weekly. Romiplostim treatment was resumed at a dose reduced by 1 mcg/kg after platelet count fell to <200000/µL.

A total of 35 adverse events (AEs) were reported by 16 (32%) of 50 patients during study. The most commonly reported AEs (incidence in ≥4% patients) were diarrhea (4%), nausea (4%), vomiting (4%), pyrexia (4%), myalgia (4%) and dysuria (4%). Adverse events reported during study are summarized in Table 3.

Table 3: Adverse Events Reported in Adult Patients with Chronic Refractory ITP Treated with Intas Romiplostim

System organ class; Preferred term	Number of AEs (% of patients)
Gastrointestinal disorders	
Constipation	1 (2%)
Diarrhoea	2 (4%)
Hyperchlorhydria	1 (2%)
Nausea	2 (4%)
Toothache	1 (2%)
Vomiting	2 (4%)
General disorders and administration site conditions	
Chest pain	1 (2%)
Pain	1 (2%)
Pyrexia	2 (4%)
Infections and infestations	
Herpes virus infection	1 (2%)
Nasopharyngitis	1 (2%)
Rhinitis	1 (2%)
Typhoid fever	1 (2%)
Injury, poisoning and procedural complications	
Animal bite	1 (2%)
Metabolism and nutrition disorders	
Decreased appetite	1 (2%)
Dehydration	1 (2%)
Musculoskeletal and connective tissue disorders	
Arthralgia	1 (2%)
Myalgia	2 (4%)
Nervous system disorders	
Headache	1 (2%)
Lacunar infarction	1 (2%)
Psychiatric disorders	
Insomnia	1 (2%)
Renal and urinary disorders	
Dysuria	2 (4%)
Respiratory, thoracic and mediastinal disorders	
Cough	1 (2%)
Epistaxis	1 (2%)
Skin and subcutaneous tissue disorders	
Dermatitis bullous	1 (2%)
Papule	1 (2%)
Swelling face	1 (2%)
Eye disorders	
Dry eye	1 (2%)
Ear and labyrinth disorders	
Vertigo	1 (2%)

In another prospective, assessor-blind, randomized, parallel group clinical study, 12 patients with chronic refractory immune thrombocytopenic purpura were randomized to receive single dose of 3 mcg/kg of Intas Romiplostim or Nplate®. Total 26 adverse events were reported in 6 patients: 9 adverse events in 3 patients from Intas Romiplostim group and 17 adverse events in 3 patients from Nplate® group. However, there was one SAE (Anaemia) reported during the study after administration of Nplate®. The causality assessment was judged as unlikely. Adverse events reported during study are summarized in Table 4.

Table 4: Adverse Events Reported in Adult Patients with Chronic Refractory ITP Treated with Single-dose of Intas Romiplostim or Nplate®

System Organ Class Preferred Term	Number of AEs (% of patients)	
	Intas Romiplostim (N=6)	Nplate® (N=6)
Blood and lymphatic system disorders		
Anaemia	0 (0.00%)	1 (16.67%)
Leucocytosis	0 (0.00%)	1 (16.67%)
Ear and labyrinth disorders		
Ear Pain	0 (0.00%)	1 (16.67%)
Vertigo	0 (0.00%)	1 (16.67%)
Endocrine disorders		
Hypothyroidism	0 (0.00%)	1 (16.67%)
Gastrointestinal disorders		
Constipation	0 (0.00%)	1 (16.67%)
Nausea	3 (50.00%)	0 (0.00%)
Vomiting	0 (0.00%)	3 (16.67%)
General disorders and administration site conditions		
Asthenia	0 (0.00%)	1 (16.67%)
Oedema	0 (0.00%)	1 (16.67%)
Pyrexia	1 (16.67%)	1 (16.67%)
Metabolism and nutrition disorders		
Hypertriglyceridemia	0 (0.00%)	1 (16.67%)
Nervous system disorders		
Headache	5 (50.00%)	2 (16.67%)
Reproductive system and breast disorders		
Menorrhagia	0 (0.00%)	1 (16.67%)
Skin and subcutaneous tissue disorders		
Erythema	0 (0.00%)	1 (16.67%)

Immunogenicity

Immunogenicity profile of Intas Romiplostim was evaluated in patients with chronic refractory ITP as part of a randomized, assessor-blind, parallel-group comparative study. Adult male or female patients with diagnosis of ITP at least 3 months before enrolment and who received at least one prior treatment for ITP were administered single SC injection of 3 mcg/kg Intas Romiplostim (n=6) or Nplate® (n=6). Post-dose blood samples up to 28 days were collected and anti-drug antibodies against romiplostim were measured. One patient each from Intas Romiplostim and Nplate group was found confirmed positive for anti-drug antibody at baseline, Day 7, Day 14 and Day 28.

Immunogenicity profile of Intas Romiplostim was also evaluated as part of prospective, open-label, multicentric, phase III study in adult patients with chronic refractory ITP who received weekly SC injection of 1 mcg/kg Intas Romiplostim

for 8 weeks. Blood samples were collected three months (or more) after initiation of romiplostim treatment. Out of samples of 19 patients, one patient had confirmed positive anti-drug antibody against romiplostim. However, no adverse event was reported and no alteration in pharmacodynamic response was observed in this patient.

Information provided below is based on innovator data.

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

The most serious adverse reactions that may occur during romiplostim 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) (Table 5). Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

Table 5: Tabular List of Adverse Reactions Reported with Romiplostim

MedDRA system organ class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infection Rhinitis***	Gastroenteritis Pharyngitis*** Conjunctivitis*** Ear infection*** Sinusitis***	Influenza Localized infection Nasopharyngitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	Multiple myeloma Myelofibrosis
Blood and lymphatic system disorders	-	Bone marrow disorder* Thrombocytopenia* Anaemia	Aplastic anaemia Bone marrow failure Leucocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal
Immune system disorder	Hypersensitivity**	Angioedema	-
Metabolism and nutrition disorders	-	-	Alcohol intolerance Anorexia Decreased appetite Dehydration Gout
Psychiatric disorders	-	Insomnia	Depression Abnormal dreams
Nervous system disorders	Headache	Dizziness Migraine Paraesthesia	Clonus Dysgeusia Hypoaesthesia Hypogeusia Neuropathy peripheral Transverse sinus thrombosis
Eye disorders	-	-	Conjunctival haemorrhage Accommodation disorder Blindness Eye disorder Eye pruritus Lacrimation increased Papilloedema Visual disturbances
Ear and labyrinth disorders	-	-	Vertigo
Cardiac disorders	-	Palpitations	Myocardial infarction Heart rate increased
Vascular disorders	-	Flushing	Deep vein thrombosis Hypotension Peripheral embolism Peripheral ischaemia Phlebitis Thrombophlebitis superficial Thrombosis Erythromelalgia
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain***	Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration
Gastrointestinal disorders	Upper abdominal pain***	Nausea Diarrhoea Abdominal pain Constipation Dyspepsia	Vomiting Rectal haemorrhage Breath odour Dysphagia Gastro-oesophageal reflux disease Haematochezia Mouth haemorrhage Stomach discomfort Stomatitis Tooth discolouration
Hepatobiliary disorders	-	-	Portal vein thrombosis Increase in transaminase
Skin and subcutaneous tissue disorders	-	Pruritus Ecchymosis Rash	Alopecia Photosensitivity reaction Acne Dermatitis contact Dry skin Eczema Erythema Exfoliative rash Hair growth abnormal Prurigo Purpura Rash papular Rash pruritic Skin nodule Skin odour abnormal Urticaria
Musculoskeletal and connective tissue disorders	-	Arthralgia Myalgia Muscle spasms Pain in extremity Back pain Bone pain	Muscle tightness Muscular weakness Shoulder pain Muscle twitching
Renal and urinary disorders	-	-	Protein urine present
Reproductive system and breast disorders	-	-	Vaginal haemorrhage
General disorders and administration site conditions	-	Fatigue Oedema peripheral Influenza like illness Pain Asthenia Pyrexia Chills Injection site reaction Peripheral swelling***	Injection site haemorrhage Chest pain Irritability Malaise Face oedema Feeling hot Feeling jittery
Investigations	-	-	Blood pressure increased Blood lactate dehydrogenase increased Body temperature increased Weight decreased Weight increased
Injury, poisoning and procedural complications	-	Contusion	-

*See section "Special Warnings and Precautions for Use"
**Hypersensitivity reactions including cases of rash, urticaria, and angioedema
***Additional adverse reactions observed in pediatric studies

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

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

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

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

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

Description of selected adverse reactions
In addition the reactions listed below have been deemed to be related to romiplostim treatment.

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

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

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

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

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

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

Progression of existing Myelodysplastic Syndromes (MDS)
In a randomized placebo-controlled trial in MDS subjects, treatment with romiplostim was prematurely stopped due to a numerical increase in cases of MDS disease progression to AML and transient increases in blast cell counts in patients treated with romiplostim compared to placebo. Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML. Overall survival was similar to placebo.

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

In an ongoing pediatric clinical trial, of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin in cohort 1 and 2 out of 4 subjects (50.0%) developed increased reticulin in cohort 2. However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Clinical trials in adult ITP patients examined antibodies to romiplostim.

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

In pediatric studies, the incidence of binding antibodies to romiplostim at any time was 7.8% (22/282). Of the 22 subjects, 2 subjects had pre-existing binding non-neutralizing romiplostim antibodies at baseline. Additionally, 2.5% (7/282) developed neutralizing antibodies to romiplostim. A total of 3.2% (9/282) subjects had binding antibodies to TPO at any time during romiplostim treatment. Of these 9 subjects, 2 subjects had pre-existing binding non-neutralizing antibodies to TPO. All subjects were negative for neutralizing activity to TPO.

In the post-marketing registry study, 19 confirmed pediatric 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 neutralizing 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 neutralizing antibodies to romiplostim. A total of 2.2% (4/184) adult patients developed binding, non-neutralizing antibody against TPO.

4.9 Overdose
Information provided below is based on innovator data.

No adverse effects were seen in rats given a single dose of 1,000 mcg/kg or in monkeys after repeated administration of romiplostim at 500 mcg/kg (100 or 50 times the maximum clinical dose of 10 mcg/kg, respectively).

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue romiplostim and monitor platelet counts. Reinitiate treatment with romiplostim in accordance with dosing and administration recommendations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Antihemorrhagics, other systemic haemostatics, ATC code: B02BX04

Mechanism of action
Romiplostim is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) to increase platelet production. The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing 2 TPO receptor-binding domains.

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

Pharmacodynamics
Pharmacodynamic profile of Intas Romiplostim was evaluated after a single dose of 3 mcg/kg in patients with chronic refractory ITP as part of a randomized, assessor-blind, parallel-group comparative study. Adult male or female patients with diagnosis of ITP at least 3 months before enrolment and who received at least one prior treatment for ITP were administered single SC injection of 3 mcg/kg Intas Romiplostim (n=6) or Nplate® (n=6). Post-dose blood samples up to 7 days were collected and change from baseline in platelet counts and proportion of patients achieving targeted platelet response (doubling of baseline platelet count and within 50 x 10^9/L to 450 x 10^9/L) in the absence of rescue medication were measured. Out of 12 patients randomized, 11 patients were included in PD evaluable set (n=5 for Intas Romiplostim and n=6 for Nplate®). Descriptive statistics for the PD parameters are presented in Table 6.

Table 6: Pharmacodynamic Parameters of Intas Romiplostim and Nplate® After Single Subcutaneous Injection of 3 mcg/kg in Chronic Refractory ITP (PD Evaluable Set)

Parameters (unit)	Intas Romiplostim (n = 5)	Nplate® (n = 6)
T_{max} (h)#	96.000 (48.000 – 168.017)^	86.317 (24.000 - 144.000)
E_{max} (10^9/L)	17 ± 30.2	12 ± 9.5
$AUEC_{0-168h}$ (10^9.h/L)	963 ± 936.8^	756 ± 671.4^

Values presented as mean ± SD for untransformed data.
#T_{max} is represented as median (min-max) value.
^N = 4.
Notes: One patient from Intas romiplostim group had all platelet count values as zero. Hence, T_{max} and $AUEC_{0-168h}$ were not calculated for the same. Two patients from Nplate® had insufficient time points for the estimation of λ_z and $AUEC_{0-168h}$.

Clinical efficacy
Information provided below is based on studies conducted with Intas Romiplostim.

Treatment of chronic refractory idiopathic thrombocytopenic purpura in adult patients
Clinical efficacy of Intas Romiplostim was evaluated in a prospective, open-label, multicentric, phase III study in adult patients with chronic refractory ITP. Male or female patients aged 18-65 years (both inclusive) with confirmed diagnosis of chronic refractory ITP at least 12 months before enrolment and who received at least 1 prior treatment for ITP were randomized to receive weekly SC injection of 1 mcg/kg Intas Romiplostim for 8 weeks. Platelet counts were performed during pre-treatment period and on weekly basis during treatment. Dose levels were adjusted based on platelet counts:

- Dose was increased by 1 mcg/kg to 5 mcg/kg if platelet count was <50000/µL.
- Dose was reduced by 1 mcg/kg if platelet count was >200000 /µL for 2 consecutive weeks.
- Patient was not dosed in case platelet count was >400000 /µL.
- Patient was assessed for the platelet count weekly. Romiplostim treatment was resumed at a dose reduced by 1 mcg/kg after platelet count fell to <200000/µL.

Primary efficacy endpoint was proportion of patients achieving platelet response (defined as a platelet count at a scheduled weekly visit of 50000/µL or more and double the platelet count from baseline in absence of rescue medication within 8 weeks) during the study. Secondary efficacy endpoints included (i) dose required to achieve targeted platelet count (50000/µL), (ii) proportion of patients with at least one dose increment, (iii) proportion of patients with at least one dose reduction and (iv) patients having platelet count ≥400000/µL.

Out of 50 patients enrolled in the study, 47 were included in per-protocol (PP) population and all 50 were included in modified intent-to-treat (mITT) population. Total 30 (63.83%) patients from PP population achieved primary efficacy endpoint. Proportion of patients with at least one dose increment decreased over the course of 8-week study. Dose required to achieve target platelet count of 50000/µL was 1 mcg/kg, 2 mcg/kg, 3 mcg/kg, 4 mcg/kg and 5 mcg/kg in 28%, 17%, 11%, 4% and 13% patients, respectively (PP population). Similar results were reported for mITT population.

Clinical efficacy of Intas Romiplostim was also evaluated in a prospective, assessor-blind, parallel-group, comparative study in adult patients with chronic refractory ITP. Twelve male or female patients aged 18-65 years (both inclusive) with diagnosis of chronic refractory ITP at least 3 months before enrolment and who received at least 1 prior treatment for ITP were randomized to receive single SC injection of 3 mcg/kg Intas Romiplostim (n=6) or Nplate® (n=6). Platelet counts were performed during pre-treatment period and on weekly basis during treatment. Post-dose blood samples up to 7 days were collected and proportion of patients achieving targeted platelet response (doubling of baseline platelet count and within 50 x 10^9/L to 450 x 10^9/L) in the absence of rescue medication were evaluated.

Efficacy of Intas Romiplostim was evaluated after a single dose of 3 mcg/kg in patients with chronic refractory ITP as part of a randomized, assessor-blind, parallel-group comparative study. Adult male or female patients with diagnosis of ITP at least 3 months before enrolment and who received at least one prior treatment for ITP were administered single SC injection of 3 mcg/kg Intas Romiplostim (n=6) or Nplate® (n=6). Post-dose blood samples up to 7 days were collected and change from baseline in platelet counts and proportion of patients achieving targeted platelet response (doubling of baseline platelet count and within 50 x 10^9/L to 450 x 10^9/L) in the absence of rescue medication were measured. One patient from Intas Romiplostim group achieved target platelet response at the end of treatment. Since dose for individual patients was not titrated optimal platelet response was not anticipated. Rescue medication was not used for any patient from Intas Romiplostim or Nplate® group.

5.2 Pharmacokinetic Properties
Information provided below is based on study conducted with Intas Romiplostim.

Pharmacokinetic (PK) profile of Intas Romiplostim was evaluated in patients with chronic refractory ITP as part of a randomized, assessor-blind, parallel-group comparative study. Adult male or female patients with diagnosis of ITP at least 3 months before enrolment and who received at least one prior treatment for ITP were administered single SC injection of 3 µg/kg Intas Romiplostim (n=6) or Nplate® (n=6). Post-dose blood samples up to 7 days were collected and serum drug concentration was measured. Descriptive statistics for the PD parameters are presented in Table 7.

Table 7: Pharmacokinetic Parameters of Intas Romiplostim and Nplate® After Single Subcutaneous Injection of 3 mcg/kg in Chronic Refractory ITP

Parameters (unit)	Intas Romiplostim (n=6)	Nplate® (n=6)
T_{max} (h)#	20.000 (2.000 - 24.000)^	4.000 (0.500 - 24.000)^
AUC_{0-168h} (ng.h/mL)	2.402 ± 3.0745^	4.469 ± 4.8414^
T_{max} (h)#	20.000 (2.000 - 24.000)^	4.000 (0.500 - 24.000)^

Values presented as mean ± SD (untransformed data).
#T_{max} is represented as median (min-max) value. ^N = 5 and ^N = 4.
Notes: One patients from Intas Romiplostim and one patient from Nplate® group had all concentration values as zero. Hence, T_{max} and AUC_{0-168h} were not calculated for the same. Terminal rate constant (λ_z) could not be estimated based on obtained concentration data for one patients from Intas Romiplostim group. Hence, AUC_{0-168h} and other elimination phase dependent parameters cannot be calculated.

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

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

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

Elimination
Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3.5 days). The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical trial, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 mcg/kg).

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

Pediatric population
Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in pediatric 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
Information provided below is based on the study conducted with Intas Romiplostim.

In a 28-day repeat-dose toxicity study, Wistar rats were administered with Intas Romiplostim at the dose levels of 31, 62 and 93 mcg/kg/week and Nplate® at the dose level of 31 mcg/kg/week by SC route. There was no adverse effect observed on the parameters such as mortality, clinical signs, body weight, food consumption, serum chemistry, organ weight, gross pathology and histopathology. No observed adverse effect level (NOAEL) of Intas Romiplostim was found to be 93 mcg/kg/week.

In a single-dose PD study, Wistar rats were administered Intas Romiplostim or Nplate® at 62 mcg/kg dose by SC route. Romiplostim treatments led to significant increase in platelet counts on Day 6 and 9 compared to baseline (pre-dose) values (p<0.05). Values reached to normal levels on Day 15. Platelet responses with Intas Romiplostim were statistically comparable to Nplate®.

Information provided below is based on innovator 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 neutralizing 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 neutralizing 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 neutralizing 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, sucrose, L-histidine, polysorbate 20, hydrochloric acid (for pH adjustment) and water for injection

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products, except those mentioned in section "Special precautions for disposal and other handling".

6.3 Shelf Life
36 months when stored at 2°C – 8°C.

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

After dilution:

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.
Once stored at room temperature, do not place back in the refrigerator. For storage conditions after reconstitution of the medicinal product, see section "Shelf life".

6.5 Nature and Contents of Container
Romiplostim 250 micrograms powder
One 5 mL USP type-1 glass vial containing 250 mcg of Romiplostim.

Romiplostim 500 micrograms powder
One 5 mL USP type-1 glass vial containing 500 mcg of Romiplostim.

Solvent: Water for injection

6.6 Special Precautions for Disposal and Other Handling

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

Romiplostim 250 micrograms powder and solvent for solution for injection
Romiplostim 250 mcg powder for solution for injection should be reconstituted with 0.72 mL sterile water for injections, yielding a deliverable volume of 0.5 mL. An additional overfill is included in each vial to ensure that 250 mcg of romiplostim can be delivered (see vial content table below).

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

Vial Content:

Romiplostim single-use vial	Total vial content of Romiplostim		Volume of sterile water for injection		Deliverable product and volume	Final concentration
250 mcg	375 mcg	add	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL
500 mcg	625 mcg	add	1.2 mL	=	500 mcg in 1.00 mL	500 mcg/mL

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

Water for injections should be injected into the vial. The vial contents may be swirled gently and inverted during dissolution. The vial should not be shaken or vigorously agitated. Generally, dissolution of romiplostim 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 "Shelf-life".

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

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

Dilution Guidelines:

Romiplostim 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 mcg	2.25 mL	125 mcg/mL
500 mcg	3.75 mL	125 mcg/mL

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

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

7. MANUFACTURED AND MARKETED BY

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