Announcement regarding harshment (safety information) in the Physician Leaflet

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך:

Name of the product: Nplate 250, 500 mcg

שם תכשיר באנגלית:

Registration No's: 145-85-33243/4

מספר רישום:

Name of the registration owner: **שם בעל הרישום Amgen Europe B.V.**

4. CLINICAL PARTICULARS

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4.2 Posology and method of administration

Dose adjustments

Dose adjustments should be based on platelet counts measured weekly until stable within the recommended range. Thereafter, platelet counts should be measured at least monthly and appropriate dose adjustments made as per the Dose Adjustment Table (Table 1) in order to maintain platelet counts within the recommended range. See Table 1 below for dose adjustment and monitoring.

Table 1. Dose Adjustment Guidance Based on Platelet Count

Platelet Count (x 10^9/L)	**Action**
Initial dose only is 1 µg/kg based on actual body weight	
< 50	Increase dose by 1 µg/kg.
>200 for 2 consecutive weeks	Reduce the dose by 1 µg/kg.
> 400	Do not dose. Continue to assess the platelet count weekly. ▪ Reinitiate therapy when the platelet count is < 200 x 10^9/L at a dose reduced by 1 µg/kg.
If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of Nplate. If the patient loses response, see section 4.4, **Loss of Response to romiplostim**.	

4. CLINICAL PARTICULARS

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4.2 Posology and method of administration

Dose adjustments

A subject's actual body weight at initiation of therapy should be used to calculate dose. The once weekly dose of romiplostim should be increased by increments of 1 µg/kg until the patient achieves a platelet count ≥ 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. A maximum once weekly dose of 10 µg/kg should not be exceeded.

Adjust the dose as follows:

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 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).
[…]	**[…]**
4.4 Special warnings and precautions for use **[…]**	**4.4 Special warnings and precautions for use** **[…]** 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.
4.8 Undesirable effects The table below presents the adverse drug reactions from the two Phase 3 placebo-controlled studies with a ≥ 5% higher patient incidence in romiplostim versus placebo. The majority of these adverse drug reactions were mild to moderate in severity.	**4.8 Undesirable effects** Summary of the safety profile Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, the overall subject incidence of all adverse reactions for romiplostim-treated subjects was

Adverse Drug Reaction	Romiplostim n = 84	Placebo n = 41
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in Extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paraesthesia	6%	0%

Other adverse drug reactions that did not show a > 5% difference between romiplostim and placebo include the following:

Headache: Headache was the most commonly reported adverse drug reaction occurring in 35% of patients receiving romiplostim and 32% of patients receiving placebo. Headache occurred at a higher incidence in splenectomized patients receiving romiplostim (43%) compared with patients receiving placebo (33%). In nonsplenectomized patients, headaches occurred in 26% of patients receiving romiplostim and 30% of patients receiving placebo. Headaches were usually mild or moderate and managed with non-narcotic analgesics.
Less common adverse drug reactions observed across the entire ITP clinical program were recurrent thrombocytopenia after cessation of treatment with some patients developing thrombocytopenia of greater severity than was present prior to romiplostim, increased bone marrow reticulin, and thrombocythemia (see section 4.4, Reoccurrence of thrombocytopenia after cessation of treatment, Increased bone marrow reticulin).

Analysis of Reported Bleeding Events Across the entire ITP clinical program, 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

91.5% (248/271). The mean duration of exposure to romiplostim in this study population was 50 weeks.

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

Tabulated list of adverse reactions

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

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

counts < 50 x 10^9/l.

In the Phase 3 studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] romiplostim, 4 [9.8%] placebo).1 Bleeding events that were grade 2 or higher were reported by 15% of patients treated with romiplostim and 34% of patients treated with placebo.2

In the Phase 3 ITP long-term safety set, the study duration adjusted event rate of grade 2 or higher bleeding events was 71 per 100 patient-years for patients treated with romiplostim and 132 per 100 patient-years for placebo treated patients.3

These trends in bleeding event rates were observed in the context of a greater reduction of concomitant ITP medications among patients receiving romiplostim relative to placebo. In addition, there was a higher incidence of rescue medication use among patients receiving placebo (see section 5.1, Clinical data).

Immunogenicity

Patients were screened for immunogenicity to romiplostim using a Biacore-based biosensor immunoassay. This assay is capable of detecting both high and low affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In clinical studies, the incidence of pre-existing antibodies to romiplostim was 8% and the incidence of binding antibody development during romiplostim treatment was 6%. The incidence of pre-existing antibodies to endogenous TPO was 5% and the incidence of binding antibody development to endogenous TPO during romiplostim treatment was 4%. Of the patients with positive antibodies to romiplostim or to TPO, 2 (0.4%) patients had neutralizing activity to romiplostim and none had neutralizing activity to TPO.

Blood and lymphatic system disorders		Bone marrow disorder* Thrombocytopenia* Anaemia	Aplastic anaemia Bone marrow failure Leukocytosis Splenomegaly Thrombocythaemia Platelet count increased Platelet count abnormal
Immune system disorder	Hypersensitivity**	Angioedema	
Metabolism and nutrition disorders			Alcohol intolerance Anorexia Decreased appetite Dehydration Gout
Psychiatric disorders		Insomnia	Depression Abnormal dreams
Nervous system disorders	Headache	Dizziness Migraine Paraesthesia	Clonus Dysgeusia Hypoaesthesia Hypogeusia Neuropathy peripheral Transverse sinus thrombosis

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

Postmarketing Experience

- Erythromelalgia
- Hypersensitivity
- Angioedema

Eye disorders			Conjunctival haemorrhage Accommodation disorder Blindness Eye disorder Eye pruritus Lacrimation increased Papilloedema Visual disturbances
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Palpitations	Myocardial infarction Heart rate increased
Vascular disorders		Flushing	Deep vein thrombosis Hypotension Peripheral embolism Peripheral ischaemia Phlebitis Thrombophlebitis superficial Thrombosis Erythromelalgia

Respiratory, thoracic and mediastinal disorders		Pulmonary embolism*	Cough Rhinorrhoea Dry throat Dyspnoea Nasal congestion Painful respiration
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Constipation Dyspepsia	Vomiting Rectal haemorrhage Breath odour Dysphagia Gastro-oesophageal reflux disease Haematochezia Mouth haemorrhage Stomach discomfort Stomatitis Tooth discolouration
Hepatobiliary disorders			Portal vein thrombosis Increase in transaminase

Skin and subcutaneous tissue disorders		Pruritus Ecchymosis Rash	Alopecia Photosensitivity reaction Acne Dermatitis contact Dry skin Eczema Erythema Exfoliative rash Hair growth abnormal Prurigo Purpura Rash papular Rash pruritic Skin nodule Skin odour abnormal Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle spasms Pain in extremity Back pain Bone pain	Muscle tightness Muscular weakness Shoulder pain Muscle twitching
Renal and urinary disorders			Protein urine present
Reproductive system and breast disorders			Vaginal haemorrhage

General disorders and administration site conditions		Fatigue Oedema peripheral Influenza like illness Pain Asthenia Pyrexia Chills Injection site reaction	Injection site haemorrhage Chest pain Irritability Malaise Face oedema Feeling hot Feeling jittery
Investigations			Blood pressure increased Blood lactate dehydrogenase increased Body temperature increased Weight decreased Weight increased
Injury, poisoning and procedural complications		Contusion	

* see section 4.4
** Hypersensitivity reactions including cases of rash, urticaria, and angioedema

Description of selected adverse reactions

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

Thrombocytosis

	Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 3 events of thrombocytosis were reported, n = 271. No clinical sequelae were reported in association with the elevated platelet counts in any of the 3 subjects. *Thrombocytopenia after cessation of treatment* Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 4 events of thrombocytopenia after cessation of treatment were reported, n = 271 (see section 4.4). *Progression of existing Myelodysplastic Syndromes (MDS)* In a randomized placebo-controlled trial in MDS subjects treatment with romiplostim was prematurely stopped due to a numerical increase in cases of MDS disease progression to AML and transient increases in blast cell counts in patients treated with romiplostim compared to placebo. Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML (see section 4.4). Overall survival was similar to placebo. *Increased bone marrow reticulin* In clinical trials, romiplostim treatment was discontinued in 4 of the 271 patients because of bone marrow reticulin deposition. In 6 additional patients reticulin was observed upon bone marrow biopsy (see section 4.4).

6. PHARMACEUTICAL PARTICULARS **[…]** **6.6 Special precautions for disposal and other handling** **[…]** **[…]**	**6. PHARMACEUTICAL PARTICULARS** **[…]** **6.6 Special precautions for disposal and other handling** **[…]** Vial Content: **[…]**

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