PrNplate® romiplostim

Eltrombopag

PrNplate® (romiplostim) thrombopoiesis-stimulating protein[1]		PrRevolade® (eltrombopag) thrombopoietin receptor agonist[2]
Once-weekly subcutaneous injection	**ADMINISTRATION**	Once-daily oral tablet
1 µg/kg based on actual body weight. Do not exceed a maximum weekly dose of 10 µg/kg. If the platelet count is < 50 x 10^9/L, increase the dose by 1 µg/kg every 1 to 2 weeks. If platelet count is > 200 x 10^9/L for 2 consecutive weeks, reduce the dose by 1 µg/kg every 2 weeks. If platelet count is > 400 x 10^9/L do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 x 10^9/L, resume at a dose reduced by 1 ug/kg.	**DOSAGE RANGE**	Recommended starting dose (adults and pediatric patients aged 6 years and above): 50 mg once daily. Initial dose should be reduced to 25 mg once daily in patients of East Asian/ Southeast Asian ancestry. Recommended starting dose (pediatric patients aged 1 to < 6 years): 25 mg once daily. If after 2 to 3 weeks of initial therapy platelet counts are < 50 x 10^9/L, dose may be increased to a maximum of 75 mg once daily. Dose reduction should be considered with platelet counts increasing to > 150 x 10^9/L. At platelet counts ≥ 200 x 10^9/L, dose reduction is recommended. If platelet counts are > 300 x 10^9/L, interrupt therapy and reinitiate at a reduced dose after the platelet count has fallen to < 150 x 10^9/L. If platelet counts remain at > 300 x 10^9/L after 2 weeks of therapy at the lowest dose, discontinue treatment.
250 µg/0.5 mL and 500 µg/1 mL vials (after reconstitution)	**AVAILABLE DOSAGE FORMS**	12.5, 25, 50, and 75 mg tablets
To increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • who are nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/or immunoglobulins; • who are splenectomized and have had an inadequate response to splenectomy. Nplate® has been used alone or in combination with other ITP therapies such as corticosteroids, azathioprine, or danazol.	**INDICATIONS**	For the treatment of chronic immune thrombocytopenia purpura (ITP) to increase platelet counts in adult and pediatric patients 1 year and older who have had an insufficient response to corticosteroids or immunoglobulins. The median duration of treatment with eltrombopag in pediatric clinical trials was 5.6 months, with a minimum duration of 0.5 months and a maximum duration of 9.0 months. The long-term safety and efficacy of eltrombopag have not been established in pediatric ITP patients. Also indicated to increase platelet counts in thrombocytopenic patients with chronic hepatitis C virus (HCV) infection to allow the initiation and maintenance of interferon-based therapy, and for the treatment of adult patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy.
No formal drug-drug interaction studies of Nplate® have been performed. ITP medical therapies used in combination with Nplate® in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulins (IVIGs), and anti-D immunoglobulin. When combining Nplate® with other ITP medical therapies, platelet counts should be monitored in order to manage unexpected changes.	**DRUG INTERACTIONS**	In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. In vitro studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. When eltrombopag and rosuvastatin were co-administered in a clinical drug interaction study, there was increased plasma rosuvastatin exposure. Interactions are also expected with other HMG CoA reductase inhibitors, including pravastatin, simvastatin, and lovastatin; however, clinically significant interactions are not expected between eltrombopag and atorvastatin or fluvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring should be undertaken. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for co-administration of rosuvastatin and eltrombopag. Concomitant administration of eltrombopag and other OATP1B1 and BCRP substrates should be undertaken with caution. Co-administration of eltrombopag with cyclosporine may cause a decrease in the concentration of eltrombopag, though the exact mechanism is unknown. Therefore, caution should be used when co-administration of eltrombopag with cyclosporine takes place. Platelet count should be monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of eltrombopag when cyclosporine therapy is initiated or discontinued. Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued. Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium, selenium, and zinc. Eltrombopag should be taken at least 2 hours before or 4 hours after any products such as antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in eltrombopag absorption. Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag concentrations. Food low in calcium (< 50 mg calcium) did not significantly impact plasma eltrombopag exposure, regardless of calorie or fat content.
Time to peak concentration: Median: 14 hours (range 7–50) **Half-life:** Median: 3.5 days (range 1–34)	**PHARMACOKINETICS**	**Time to peak concentration:** 2–6 hours **Half-life:** Approximately 21–32 hours
There is a lack of studies conducted in patients with renal impairment; use with caution in this population.	**RENAL IMPAIRMENT**	Patients with renal impairment may have decreased exposure to eltrombopag. Eltrombopag should be used with caution in patients with impaired renal function, and close monitoring should be performed, for example, by testing serum creatinine and/or urinalysis. There are limited data with the use of eltrombopag in patients with severe renal impairment (creatinine clearance < 30 mL/min) therefore it is generally not recommended for use in these patients.
There is a lack of studies conducted in patients with hepatic impairment; use with caution in this population.	**HEPATIC IMPAIRMENT**	Eltrombopag is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C). Exercise caution when administering eltrombopag to patients with mild or moderate hepatic impairment, since exposure to eltrombopag increases with increasing degrees of hepatic dysfunction. The risk of thromboembolic events of the portal venous system has been found to be increased in patients with chronic liver disease treated with 75 mg eltrombopag once daily for 2 weeks in preparation for invasive procedures. Eltrombopag should not be used in ITP or SAA patients with hepatic impairment (Child-Pugh Classes A and B) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If the use of eltrombopag is deemed necessary in adult ITP or SAA patients with liver impairment (Child-Pugh Classes A and B), the starting dose must be 25 mg once daily. Attempts to maintain platelet counts below 200 x 10^9/L should be carried out in this patient population. There are no data in pediatric patients with hepatic impairment. After initiating eltrombopag or following any dose increase in ITP patients with liver impairment (Child-Pugh Classes A and B), wait a minimum of 3 weeks before increasing the dose. Thrombocytopenic patients with chronic hepatitis C virus should initiate eltrombopag at the usual dose of 25 mg once daily.
Monitor complete blood counts (CBCs), including platelet counts, prior to initiation, throughout, and following discontinuation of Nplate® therapy. Prior to the initiation of Nplate®, examine the peripheral blood differential to establish the baseline extent of red and white blood cell abnormalities. Obtain CBCs, including platelet counts, weekly during the dose adjustment phase of Nplate® therapy and then monthly following establishment of a stable Nplate® dose. Obtain CBCs, including platelet counts, weekly for at least two weeks following discontinuation of Nplate®.	**MONITORING AND LABORATORY TESTS**	**Complete blood counts (CBC):** Monitor CBC, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of therapy with eltrombopag. Prior to the initiation of eltrombopag, examine the peripheral blood differential to establish the extent of red and white blood cell abnormalities. Obtain CBC, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with eltrombopag and then monthly following establishment of a stable dose of eltrombopag. The dose of eltrombopag may need to be modified based on platelet counts. Examine the monthly peripheral blood smears and CBC for new or worsening morphologic abnormalities or cytopenia(s); if present, discontinue treatment with eltrombopag and consider a bone marrow biopsy, including staining for fibrosis. Obtain CBC, including platelet counts, weekly for 4 weeks following discontinuation of eltrombopag. **Liver tests:** Monitor serum liver tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) prior to initiation of eltrombopag, then every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormalities resolve, stabilize, or return to baseline levels. Discontinue eltrombopag if important liver test abnormalities occur. **Bone marrow examination:** For ITP patients, consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs such as increased peripheral blast cell. For SAA patients who have an insufficient response to immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. Discontinuation of eltrombopag should be considered if new cytogenetic abnormalities are observed.

Data from separate Product Monographs. Comparative clinical significance has not been established.

Mechanism of action*

PrNplate®		Eltrombopag
Nplate® increases platelet production through binding and activation of the thrombopoietin receptor, a mechanism analogous to endogenous thrombopoietin (eTPO).	**MECHANISM OF ACTION**	Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous TPO, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

TPO: thrombopoietin; TPO-R: thrombopoietin receptor
*Clinical significance unknown.

Data from separate Product Monographs.
Comparative significance has not been established.

For reconstitution guidance and additional information about Nplate®, please visit **amgen.ca/nplatevideo/.**

References:
1. Nplate® Product Monograph. Amgen Canada Inc. May 6, 2020.
2. Revolade® Product Monograph. Novartis Pharmaceuticals Canada Inc. May 15, 2019.

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, ON L5N 0A4

NPL06021E

Contraindications:
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container
- Known history of sensitivity or allergy to any *E. coli*-derived product

Most serious warnings and precautions:
- **Myelodysplastic syndromes:** not for use in these patients
- **Risk of serious bleeding:** patients should be closely monitored during treatment and rescue medications might be required
- **Thrombocytopenia recurrence, sometimes markedly below pre-treatment baseline levels, and serious life-threatening or fatal bleeding** have been reported after discontinuation of Nplate® (monitoring is recommended)

Other relevant warnings and precautions:
- For use only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk of bleeding
- Should not be used in an attempt to normalize platelet counts
- Risk of development or progression of reticulin fibre deposition within the bone marrow and bone marrow fibrosis with cytopenias (monitoring is recommended)
- Risk of thrombotic/thromboembolic complications with excessive doses of Nplate® or medication errors (monitoring is recommended)
- Caution in patients with known risk factors for thromboembolism and chronic liver disease
- Increased risk of hematologic malignancies
- Laboratory monitoring of CBCs, including platelet counts, prior to initiation, throughout and following discontinuation of Nplate®
- Peripheral blood differential prior to initiation
- Safety and efficacy of Nplate® have not been established in pediatric patients
- Caution in patients with hepatic or renal impairment
- Lack or loss of response to Nplate® (search for causative factors)
- Malignancies and progression of malignancies
- Medication errors including overdose and underdose have been reported
- It is not known whether Nplate® is present in human milk. Caution should be exercised when Nplate® is administered in women who are breastfeeding
- Safety and efficacy of Nplate® in pregnant women have not been established. Nplate® should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus

For more information:
Please consult the Product Monograph at http://www.amgen.ca/Nplate_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing that has not been discussed in this piece.

The Product Monograph is also available by calling 1-866-502-6436.

A COMPARISON OF TPO MIMETICS*

Nplate® romiplostim

*TPO mimetics: thrombopoietin mimetics
Data from separate Product Monographs.
Comparative clinical significance has not been established.

Nplate® romiplostim & Eltrombopag