

**Criteria for Use: Thrombopoietin Agonists  
Eltrombopag (Promacta®) and Romiplostim (Nplate®)  
VA Pharmacy Benefits Management Services, Medical Advisory Panel,  
and VISN Pharmacist Executives**

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

FDA-Approved Indication: Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who had an insufficient response to corticosteroids, immune globulins or splenectomy. (For details, refer to the monographs: <http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Drug%20Monographs/Eltrombopag.doc>; [http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Drug%20Monographs/Romiplostim%20\(Nplate\)%20Drug%20Monograph.doc](http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Drug%20Monographs/Romiplostim%20(Nplate)%20Drug%20Monograph.doc))

**EXCLUSION CRITERIA (If any are selected below, patient is not eligible for either drug)**

- 1. Active malignancy or stem cell disorder
- 2. Patient has not received prior therapy as an attempt to increase platelet counts
- 3. Thrombocytopenia secondary to bone marrow suppressive anticancer therapy, antibiotic therapy or other drugs
- 4. Thrombocytopenia secondary to chronic liver disease
- 5. Patient refuses to transfer hematology care to VA hematology/oncology provider
- 6. Thromboembolic event within the prior year, unless evaluated by a hematology provider and deemed to be an appropriate candidate
- 7. Patient is unable to comprehend and/or comply with dosing instructions
- 8. Patient is non-compliant with appointments for blood work

**INCLUSION CRITERIA (Criterion #1, 2 and 3 must be met)**

- 1. Documented diagnosis of Idiopathic Thrombocytopenia Purpura (ITP), per American Society of Hematology (ASH) guidelines\*
- 2. Platelet count < 30,000 mm<sup>3</sup> with high bleed risk characteristics per ASH guidelines \*\*
- 3. Patient has failed to respond to at least two (2) prior therapies listed:
  - Corticosteroids (unless contraindicated)
  - Immune globulin (unless contraindicated)
  - Splenectomy (unless contraindicated)
  - Cytotoxic therapy (ie. azathioprine, cyclophosphamide, vincristine)
  - Immune suppressant therapy (ie. cyclosporine, mycophenolate mofetil, rituximab)
  - Other (ie. danazol)

\* Diagnosis of ITP is based on history, PE, CBC and exam of peripheral smear. Bone marrow aspiration is appropriate in patients over age 60 years and those considering splenectomy (Blood 1996; 88: 3)

\*\* High bleed risk characteristics include age ≥ 60 yrs and/or major risk factors for bleeding such as hypertension, peptic ulcer disease or a vigorous lifestyle (Blood 1996; 88: 3)

**DOSAGE AND ADMINISTRATION**

	<b>ELTROMBOPAG</b>	<b>ROMIPLOSTIM</b>
<b>Initial dose</b> East Asian descendent Mod-severe hepatic insufficiency	50 mg orally once daily 25 mg orally once daily 25 mg orally once daily	1 mcg/kg (ABW) SQ weekly
<b>Dose adjustments based on platelet count</b>		
< 50 x 10 <sup>9</sup> /L	↑ daily dose by 25mg to maximum <sup>+</sup>	↑ weekly dose by 1 mcg/kg
200 – 400 x 10 <sup>9</sup> /L	↓ daily dose by 25mg <sup>+</sup>	↓ weekly dose by 1 mcg/kg
> 400 x 10 <sup>9</sup> /L	Hold eltrombopag <sup>++</sup>	Hold romiplostim
<b>Maximum dose</b>	75 mg/day	10 mcg/kg/week

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<b>Notes</b>	<p>+ Assess impact of dose adjustment following at least 2 weeks of eltrombopag therapy.</p> <p>** Increase frequency of platelet monitoring to twice weekly. Once platelet count &lt; 150 x 10<sup>9</sup>/L, reinitiate therapy at daily dose reduced by 25 mg.</p>
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## RECOMMENDED MONITORING

<b>ELTROMBOPAG</b>	<b>ROMIPILOSTIM</b>
<p>Monitoring prior to initiation of therapy</p> <ul style="list-style-type: none"> <li>Peripheral blood smear</li> <li>Ocular exam</li> <li>Serum liver tests (Tbili, AST, ALT)</li> <li>CBC</li> </ul>	<p>Monitoring prior to initiation of therapy</p> <ul style="list-style-type: none"> <li>Peripheral blood smear</li> <li>CBC</li> </ul>
<p>Monitoring during therapy</p> <ul style="list-style-type: none"> <li>Peripheral blood smear weekly until stable, then monthly</li> <li>CBC weekly until stable, then monthly</li> <li>Serum liver tests every 2 wks until stable, then monthly</li> </ul>	<p>Monitoring during therapy</p> <ul style="list-style-type: none"> <li>Peripheral blood smear weekly until stable, then monthly</li> <li>CBC weekly until stable, then monthly</li> </ul>
<p>Monitoring upon discontinuation of therapy</p> <ul style="list-style-type: none"> <li>CBCs weekly for at least four weeks</li> </ul>	<p>Monitoring upon discontinuation of therapy</p> <ul style="list-style-type: none"> <li>CBCs weekly for at least four weeks</li> </ul>

## ISSUES FOR CONSIDERATION

- Eltrombopag and romiplostim are non-formulary items.
- Patients considered high risk for thromboembolism. TPO agonists may further increase risk for thrombotic complications. Consider risk of potential thromboembolic event vs. benefit of reducing bleed risk in these cases.
- Drug-drug interactions
  - Eltrombopag: Multiple interactions reported. Eltrombopag is a substrate of CYP1A2 and CYP2C8; an inhibitor of OATP1B1; an inhibitor of UDP-glucuronosyltransferases (UGTs); and chelates polyvalent cations. Refer to prescribing information for details of interactions and management (<http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Drug%20Monographs/Eltrombopag.doc>)
  - Romiplostim: None known
- Drug-food interactions
  - Eltrombopag: Separate ingestion of food containing iron, calcium, aluminum, magnesium, selenium and zinc by at least 4 hours.
  - Romiplostim: None known
- Non-responders
  - Consider discontinuing romiplostim after four weeks at maximum dose (10 mcg/kg/wk) if platelet count has not increased to a sufficient level to prevent bleeding.
  - Consider discontinuing eltrombopag after 6 weeks at maximum dose (75 mg/day) if platelet count has not increased to a sufficient level to prevent bleeding.
- Renal insufficiency
  - Eltrombopag: safety/efficacy not studied; use with caution in those with renal impairment
  - Romiplostim: safety/efficacy not studied; use with caution in those with renal impairment
- Hepatic insufficiency
  - Eltrombopag: clearance reduced in moderate-severe hepatic impairment; initial dose should be reduced to 25mg PO daily; monitor serum liver function tests as recommended
  - Romiplostim: safety/efficacy not studied; use with caution in those with hepatic impairment
- Pregnancy or Nursing mothers
  - Pregnancy Category C. Consider potential benefit to mother against potential risk to fetus.
- REMS programs; enrollment for patients, providers and institutions; for details, refer to <http://vaww.national.cmop.va.gov/PBM/Special%20Handling%20Drugs/Forms/AllItems.aspx>
  - Eltrombopag: Promacta CARES
  - Romiplostim: NEXUS

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## TPO Agonist Comparison: Eltrombopag and Romiplostim

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<b>Parameter</b>	<b>Eltrombopag</b>	<b>Romiplostim</b>
Trade name	Promacta®	Nplate®
Drug class	TPO agonist	TPO agonist
Formulation	Oral tablet	Subcutaneous injection
Preparation	Empty stomach; Separate doses from antacids, dairy products and mineral supplements	Reconstitute vial; Measure and withdraw dose; Prepare injection site
Dose	Fixed	Weight-based (using actual wgt)
Dosing frequency	Daily	Weekly
Dose adjustment	East Asian ethnicity; Hepatic impairment; Platelet response	Platelet response
FDA-approved indication	Chronic ITP, for those with insufficient response to corticosteroids, immune globulin or splenectomy	Chronic ITP, for those with insufficient response to corticosteroids, immune globulin or splenectomy
Off-label uses	Chemo-induced thrombocytopenia, thrombocytopenia assoc with HCV treatment	Chemo-induced thrombocytopenia, thrombocytopenia assoc with HCV treatment, thrombocytopenia assoc with MDS
Baseline monitoring	CBC; Peripheral blood smear; Serum liver tests (AST, ALT, Tbili); Ocular examination	CBC; Peripheral blood smear
Monitoring During therapy	CBC; Peripheral blood smear; Serum liver tests	CBC; peripheral blood smear
Precautions	Bone marrow reticulin formation; Worsening thrombocytopenia; Thrombosis/thromboembolism; Hematologic malignancies; Risk for hepatotoxicity; Cataracts	Bone marrow reticulin formation; Worsening thrombocytopenia; Thrombosis/thromboembolism; Hematologic malignancies; Lack or loss of response
Drug interactions	Substrate of CYP1A2, CYP2C8; Inhibitor of OATP1B1 Inhibitor of UGT1A1, UGT 1A3, UGT1A4, UGT 1A6, UGT 1A9, UGT 2B7, UGT 2B15 Chelates polyvalent cations (iron, calcium, magnesium, aluminum, selenium, zinc)	None known
Food interactions	Separate food containing iron, calcium, aluminum, magnesium, selenium and zinc by at least 4 hrs	None known
REMS program	Promacta CARES program enrolls prescribers, pharmacies and patients	NEXUS program enrolls prescribers, patients and institutions

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