Thrombopoiesis Stimulating Proteins
Therapeutic Class Review (TCR)

September 18, 2018

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.
### FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>avatrombopag (Doptelet&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Akarx/Dova</td>
<td>Treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure</td>
</tr>
<tr>
<td>eltrombopag (Promacta&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Novartis</td>
<td>Treatment of thrombocytopenia in adult and pediatric patients ≥ 1 year of age with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Eltrombopag should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of thrombocytopenia in patients with chronic hepatitis C (HCV) to allow the initiation and maintenance of interferon-based therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Eltrombopag should be used only in patients with chronic HCV whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic HCV genotype 1 infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eltrombopag is not indicated for the treatment of myelodysplastic syndrome (MDS)</td>
</tr>
<tr>
<td>fostamatinib disodium hexahydrate (Tavalisse™)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Rigel</td>
<td>Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment</td>
</tr>
<tr>
<td>lusutrombopag (Mulpleta&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Shionogi</td>
<td>Treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure</td>
</tr>
<tr>
<td>romiplostim (Nplate&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Amgen</td>
<td>Treatment of thrombocytopenia in patients with chronic ITP who have failed to achieve an adequate response with corticosteroids, immunoglobulins, or splenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Romiplostim should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases their risk for bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Romiplostim should not be used in an attempt to normalize platelet counts</td>
</tr>
</tbody>
</table>
OVERVIEW\textsuperscript{6,7}

Platelets are small, circulating cell particles that do not contain a nucleus. Platelets are released into the bloodstream by megakaryocytes that reside in the bone marrow. Platelets function to maintain hemostasis by aggregating and forming platelet plugs at sites of injury to limit blood loss.

Thrombocytopenia is generally defined as a platelet count of $< 100 \times 10^9$/L\textsuperscript{8}. Thrombocytopenia can result in bruising, bleeding, and fatal hemorrhaging. Causes of thrombocytopenia include decreased bone marrow production of megakaryocytes, splenic sequestration of platelets, and increased destruction of platelets.

Until 2009, the definitions, terminology, and outcome parameters of thrombocytopenia have widely varied in clinical trials and literature.\textsuperscript{9} Established by an international working group, the term “ITP” now refers to the immune thrombocytopenia, which requires a platelet count of $< 100 \times 10^9$/L. Prior to its current definition, ITP was also known as “immune thrombocytopenic purpura” and “idiopathic thrombocytopenic purpura.”\textsuperscript{10,11}

ITP is an immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system. In children, ITP is usually an acute, self-limiting disease that often occurs 2 to 3 weeks after a viral infection or immunization. Spontaneous remission in children typically occurs within 2 to 8 weeks. In adults, ITP has an insidious onset with no preceding viral or other illness and typically has a chronic course. Many adult cases of ITP are diagnosed incidentally after a routine complete blood count (CBC). Signs and symptoms of ITP are highly variable and range from asymptomatic with mild bruising or mucosal bleeding to frank hemorrhage from any site. Severity of ITP in adults is dependent on the presence of active bleeding; platelet count; patient age; patient’s lifestyle related to risk of bleeding; and presence of additional risk factors for bleeding, such as uremia or chronic liver diseases.

Primary ITP is defined as an autoimmune disorder with isolated thrombocytopenia ($< 100 \times 10^9$/L) in the absence of other causes or disorders that might cause thrombocytopenia. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present. Primary ITP is also defined by the length of time since diagnosis – newly diagnosed ($< 3$ months), persistent (between 3 and 12 months), and chronic ($\geq 12$ months). Secondary causes of ITP include drug-induced, autoimmune diseases such as systemic lupus erythematosus (SLE), and viral infections such as human immunodeficiency virus (HIV) and Hepatitis C.\textsuperscript{12,13} Severe ITP, occurring at any time, indicates bleeding which requires treatment or the occurrence of new bleeding symptoms, which requires additional treatment or increased dose to control bleeding.

In 2010, an international consensus report on primary ITP provided a review of updated therapies for the management of ITP.\textsuperscript{14} Not all patients with ITP require treatment. Treatment decisions depend on the presence or absence of bleeding, platelet count, and assessment of risk factors for bleeding. In adults, corticosteroids, particularly prednisone, continue to be first-line therapy for the treatment of ITP. Intravenous gammaglobulin (IVIG) infusions may induce a response faster than corticosteroids. Intravenous anti-RhO (D)/anti-D may be an effective alternative; however, these products cannot be used for Rh-negative or post-splenectomy patients. Although not approved for the treatment of ITP, second-line therapies include azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone,
mycophenolate mofetil, rituximab, splenectomy, thrombopoietin agonists, and vinca alkaloids. Treatment for patients failing first- and second-line therapies includes thrombopoietin receptor agonists (TBO-RA) which have sufficient data to support their use and other therapies which, have minimal data to support their use and are considered to have potential for considerable toxicity. For supportive therapy, fibrinolysis inhibitors may be used to reduce excessive mucous membrane hemorrhages, such as nasal, gastrointestinal, and urinary tract bleeding and menorrhagia. Platelet transfusions are effective if no platelet antibodies are present. Massive bleeding is compensated with red cells, fresh-frozen plasma, and platelet concentrates.

Chronic refractory ITP is defined as failure of response following splenectomy and additional therapy is required. About 20% to 30% of adult patients with ITP have chronic refractory ITP.

The American Society of Hematology (ASH) released 2011 evidence-based practice guidelines for the management of immune thrombocytopenia. For adults, treatment for a newly diagnosed patient is considered at a platelet count of < 30 × 10^9/L (grade 2C). Treatment decisions should consider the presence and severity of bleeding, the rapidity of desired platelet count rise, and the possible adverse effects. In the management of adults with ITP, first-line treatment includes longer courses of corticosteroids (such as prednisone 1 mg/kg orally for 21 days then tapered off) over shorter courses of corticosteroids or IVIG as first-line treatment (grade 2B). IVIG may be used with corticosteroids when a more rapid increase in platelet count is necessary (grade 2B). Either IVIG or anti-D (in appropriate patients) may be used as a first-line therapy if corticosteroids are contraindicated (grade 2C). If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. IVIG may be repeated if necessary (grade 2B).

The ASH guidelines recommend splenectomy for patients who are unresponsive to or relapse after initial corticosteroid therapy (grade 1B). Thrombopoietin receptor agonists may be considered for patients at risk for bleeding who have failed at least 1 other therapy and who relapse after splenectomy or have a contraindication to splenectomy (grade 1B). Thrombopoietin receptor agonists may also be considered in patients at risk for bleeding who have not had a splenectomy and who have failed one line of therapy such as corticosteroids or IVIG (grade 2C). For adult patients after splenectomy, no treatment is recommended if the platelet count exceeds 30 × 10^9/L (grade 1C). Fostamatinib was not available at the time of this guideline development.

Thrombocytopenia occurs in 64% to 84% of patients chronic liver disease (CLD) with cirrhosis or fibrosis and approximately 6% of CLD patients without cirrhosis, making it the most common hematologic abnormality found in patients with CLD. Liver disease-related thrombocytopenia is thought to generally be caused by decreased production (e.g., reduced thrombopoietin), splenic sequestration, and increased destruction of platelets. Patients with CLD often require invasive procedures and are at increased risk of bleed related to the procedures. Interventional management (e.g., partial splenic embolization [PSE], surgical splenectomy) have been used in an attempt to correct splenomegaly-associated thrombocytopenia; however, the only non-invasive tool to increase platelet count is platelet transfusion, which has risks for allergic reaction, infection, and iron overload if used chronically. While there are guidelines available for platelet transfusions in adults and thrombocytopenia treatment recommendations for patients with cancer or immune (idiopathic) thrombocytopenia (ITP), there are no specific guidelines for the treatment of thrombocytopenia in CLD patients who are undergoing an invasive procedure. Avatrombopag and lusutrombopag have been proven efficacious for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure.
Avatrombopag (Doptelet), eltrombopag (Promacta), and lusutrombopag (Mulpleta) are oral thrombopoietin receptor agonists (TPO-RA) that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

TPO-RAs produce dose- and exposure-dependent platelet increases. With avatrombopag, onset has been reported within 3 to 5 days of the start of a 5-day treatment course, with peak effect occurring after 10 to 13 days. Upon discontinuation of avatrombopag, platelet counts gradually decrease to near baseline values after 35 days. For lusutrombopag, median time to reach maximum platelet count was 12 days (range, 5 to 35).

Eltrombopag does not affect platelet aggregation or platelet activation. In healthy volunteers, eltrombopag increased platelet counts in a dose-dependent manner with platelet counts rising within 1 to 2 weeks after therapy had begun.

Fostamatinib is a spleen tyrosine kinase inhibitor (SYK). In vivo, fostamatinib disodium hexahydrate salt converts to its pharmacologically active metabolite, R406, which inhibits signal transduction of Fc-activating receptors and B-cell receptor resulting in reduced antibody-mediated platelet destruction.

Romiplostim (Nplate) increases platelet production through binding and activation of the thrombopoietin receptor in a manner that is similar to endogenous thrombopoietin. Romiplostim is a recombinant thrombopoiesis-stimulating Fc-peptide fusion protein. The peptide portion binds to and activates the human thrombopoietin receptor. Although romiplostim is a competitive thrombopoietin receptor binder, it exerts an enhanced effect on megakaryocytic colony–forming unit growth in the presence of endogenous thrombopoietin. Romiplostim is not identical to endogenous thrombopoietin. Romiplostim produces dose-dependent increases in platelet counts in healthy subjects and in patients with ITP. Platelet counts increase over 4 to 9 days with the peak occurring after 12 to 16 days of a single dose. Platelet counts return to baseline by day 28. Platelets generated by romiplostim have normal platelet function. No change in platelet aggregation has been observed.

**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Half-Life</th>
<th>Excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>avatrombopag (Doptelet)</td>
<td>nd</td>
<td>19 hours</td>
<td>Feces: 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine: 6</td>
</tr>
<tr>
<td>eltrombopag (Promacta)</td>
<td>≥ 52</td>
<td>26-35 hours</td>
<td>Feces: 59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine: 31</td>
</tr>
<tr>
<td>fostamatinib disodium hexahydrate</td>
<td>55</td>
<td>15 hours (R406)</td>
<td>Feces: 80</td>
</tr>
<tr>
<td>(Tavalisse)</td>
<td></td>
<td></td>
<td>Urine: 20</td>
</tr>
<tr>
<td>lusutrombopag (Mulpleta)</td>
<td>nd</td>
<td>27 hours</td>
<td>Feces: 83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine: 1</td>
</tr>
<tr>
<td>romiplostim (Nplate)</td>
<td>nd</td>
<td>median: 3.5 days</td>
<td>Dependent on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 1 day to 34</td>
<td>the thrombopoiesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>days</td>
<td>receptor on platelets</td>
</tr>
</tbody>
</table>

nd = no data
CONTRAINDICATIONS/WARNINGS

Contraindications

There are no known contraindications to avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta), fostamatinib (Tavalisse), or romiplostim (Nplate) therapy.

Warnings

Eltrombopag has boxed warnings regarding the risk for hepatotoxicity. Eltrombopag may increase the risk of hepatic decompensation and death when used in combination with interferon and ribavirin in patients with chronic HCV infection. Patients with albumin levels < 3.5 g/dL or a model for end-stage liver disease (MELD) score > 10 are more likely to develop hepatic decompensation and should be monitored. See the Dosage section of this review for monitoring details.

TPO receptor agonists (TPO-RA) have been associated with thrombotic and thromboembolic complications, including portal vein thrombosis, in patients with CLD. In addition, excessive doses of eltrombopag or romiplostim may increase platelet counts to a level that produces thrombotic/thromboembolic complications. Use caution when administering avatrombopag, eltrombopag, or lusutrombopag to patients with known risk factors for thromboembolism, such as Factor V Leiden, prothrombin 20210A, antithrombin deficiency, or Protein C or S deficiency. The TPO-RAs and romiplostim should not be administered in an attempt to normalize platelet counts.

Romiplostim stimulation of the thrombopoietin receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In clinical trials with romiplostim, progression from myelodysplastic syndromes (MDS) to acute myelogenous leukemia (AML) has been observed. Romiplostim is not indicated for thrombocytopenia due to MDS or any other causes of thrombocytopenia other than chronic ITP. Similarly, eltrombopag is not indicated for the treatment of thrombocytopenia due to causes other than chronic ITP (e.g., chemotherapy or myelodysplasia).

Use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., ATIII deficiency, Factor V Leiden, antiphospholipid syndrome). In clinical trials with eltrombopag in patients with non-ITP thrombocytopenia and chronic liver disease who were undergoing elective invasive procedures, the risk of thrombotic events was increased in patients receiving eltrombopag 75 mg daily. The thrombotic events in the eltrombopag group involved the portal venous system.

Eltrombopag and romiplostim increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Prior to initiation of either agent, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Once a stable romiplostim or eltrombopag dose has been established, peripheral blood smears and CBC should be examined monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If new or worsening morphological abnormalities or cytopenia(s) develop, discontinue treatment with romiplostim or eltrombopag and consider a bone marrow biopsy, which includes staining for fibrosis.

Hyporesponsiveness or failure to maintain a platelet response to romiplostim should be investigated; consider investigation for the presence of neutralizing antibodies to romiplostim or bone marrow fibrosis.
Discontinuation of eltrombopag and romiplostim may result in thrombocytopenia of greater severity than was present prior to therapy resulting in an increased bleeding risk, particularly if therapy is discontinued while the patient is on anticoagulants or antiplatelet agents. This worsened thrombocytopenia generally resolves within 14 days following cessation of romiplostim therapy. Therefore, weekly CBCs, including platelet counts, should be monitored for ≥ 2 weeks following discontinuation of romiplostim therapy or for ≥ 4 weeks following discontinuation of eltrombopag. Alternative treatments for worsening thrombocytopenia according to current treatment guidelines may be considered.

Eltrombopag may cause cataracts to develop or worsen in some patients. Perform a baseline ocular examination prior to administration of eltrombopag and during therapy with eltrombopag.

Hypertension, neutropenia, elevated liver function tests (ALT, AST, bilirubin), and diarrhea, including severe cases, have been reported with fostamatinib. Dose interruption, reduction, or discontinuation may be required.

**Risk Evaluation and Mitigation Strategy (REMS)**

Romiplostim is subject to a REMS program. The goal of the REMS is to inform healthcare providers about the risks of progression of MDS to AML, thrombotic/thromboembolic complications, bone marrow reticulin formation, bone marrow fibrosis, worsened thrombocytopenia after cessation of romiplostim, and romiplostim medication errors associated with serious outcomes. The medication guide is included in the approved product labeling.

**DRUG INTERACTIONS**

Avatrombopag (Doptelet) weakly induces CYP2C8 and CYP2C9 and inhibits organic anion transporter (OAT) 3 and breast cancer resistance protein (BCRP) in vitro. Avatrombopag is a substrate for P-glycoprotein (P-gp) mediated transport. The impact of these effects have not been fully elucidated, and the prescribing information does not detail drug interactions.

Very limited drug interaction studies were performed with eltrombopag (Promacta) and romiplostim (Nplate) agents. No formal drug interaction studies with romiplostim (Nplate) have been performed.

In vitro studies show that eltrombopag (Promacta) is an inhibitor of the organic anion transporting polypeptide, OATP1B1, and may increase the systemic exposure of other medications that are substrates of these transporters (e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, pitavastatin, pravastatin, olmesartan, rosuvastatin, repaglinide, rifampin, simvastatin, valsartan). In clinical trials, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag. Use caution with concomitant use of eltrombopag and BCRP substrates (e.g., imatinib, irinotecan, lopinavir, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients for signs and symptoms of excessive exposure to OATP1B1 or BCRP substrates when coadministered with eltrombopag.

According to in vitro studies, eltrombopag is also metabolized by CYP1A2 and CYP2C8; therefore, strong inhibitors of these 2 enzymes may result in excessive exposure of eltrombopag. Inhibitors of CYP1A2 include ciprofloxacin and fluvoxamine, and inducers include tobacco and omeprazole. Inhibitors of CYP2C8 include gemfibrozil, trimethoprim, and inducers include rifampin.
Eltrombopag is also an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 enzymes, which are involved with the metabolism of multiple drugs such as acetaminophen, narcotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies have not evaluated the significance of inhibition of these enzymes and the potential for increased systemic exposure of drugs that are substrates of UGT enzymes following their coadministration with eltrombopag. Patients should be monitored closely for signs and symptoms of excessive drug exposure when substrates of the UGT enzymes are administered with eltrombopag.

Eltrombopag chelates polyvalent cations (such as aluminum, magnesium, iron, calcium, zinc, and selenium) in antacids, mineral supplements, and food. In order to avoid significant reductions in eltrombopag due to chelation, the medication should be taken ≥ 2 hours before or 4 hours after of any medications or substances containing polyvalent cations.

For fostamatinib, CYP3A4 and UGT1A9 are involve in the metabolism of R406. R406 is a substrate of P-gp and can inhibit CYP3A4 and BCRP. Concurrent use of fostamatinib with strong CYP3A4 inhibitors (e.g., ketoconazole) increases the exposure to the major active metabolite of fostamatinib. Dose reductions may be required. Concomitant use with strong CYP3A4 inducers is not recommended due to reduction of fostamatinib metabolite levels. Concomitant use of fostamatinib may increase serum levels of substrates of CYP3A4 (e.g. simvastatin), BCRP (e.g., rosuvastatin), and P-gp (e.g., digoxin). Monitor for toxicities of these agents.

In *in vitro* studies, lusutrombopag demonstrated a low potential to inhibit or induce CYP enzymes or inhibit P-gp, BCRP, or OAT1B enzymes.

No formal drug interactions have been performed with romiplostim (Nplate).

**ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Headache</th>
<th>Diarrhea</th>
<th>Dizziness</th>
<th>Arthralgia</th>
<th>Myalgia</th>
<th>Edema</th>
<th>Increased liver enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ALT</td>
</tr>
<tr>
<td>avatrombopag</td>
<td>6 (6)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>0.4</td>
<td>3 (2)</td>
<td>nr</td>
</tr>
<tr>
<td>(Doptelet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eltrombopag</td>
<td>10</td>
<td>9-19 (2-11)</td>
<td>nr</td>
<td>nr</td>
<td>5 (2)</td>
<td>nr</td>
<td>5-6 (3)</td>
</tr>
<tr>
<td>(Promacta)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fostamatinib</td>
<td>nr</td>
<td>31 (15)</td>
<td>11 (8)</td>
<td>1</td>
<td>nr</td>
<td>nr</td>
<td>11 (0)</td>
</tr>
<tr>
<td>(Tavalisse)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lusutrombopag</td>
<td>5 (4)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>(Mulpleta)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>romiplostim</td>
<td>35 (32)</td>
<td>nr</td>
<td>17 (0)</td>
<td>26 (20)</td>
<td>14 (2)</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>(Nplate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for placebo groups are indicated in parentheses. nr = not reported. ALT = alanine aminotransferase. AST = aspartate aminotransferase.
The most common adverse effects reported in clinical trials for avatrombopag and at rates greater than placebo (rates compared to placebo) were pyrexia (10% versus 9%), abdominal pain (75% versus 6%), and fatigue (4% versus 3%).

Adverse reactions frequently reported in clinical trials with fostamatinib include (fostamatinib versus placebo): hypertension (28% versus 13%), nausea (19% versus 8%), respiratory infection (11% versus 6%), rash (9% versus 2%), fatigue and chest pain (both 6% versus 2%), and neutropenia (6% versus 0%). Mean treatment-related increases of 2.93 mmHg in systolic blood pressure and 3.53 mmHg in diastolic blood pressure over placebo were associated with fostamatinib doses of 100 mg twice daily for 28 days.

The most common serious adverse reaction reported while using eltrombopag was hemorrhage, which resulted in discontinuation of therapy.

Additional adverse effects reported with romiplostim (≥ 10% and greater than placebo) include (rates compared to placebo): insomnia (16% versus 7%), extremity pain (14% versus 5%), and abdominal pain (11% versus 0%).

**SPECIAL POPULATIONS**

**Pediatrics**

Safety and effectiveness have not been established in pediatric patients for any product in this category, with the exception of eltrombopag for the treatment of ITP in patients < 1 year of age.

**Geriatrics**

Clinical studies for avatrombopag and lusutrombopag did not include adequate numbers of patients ≥ 65 years of age to establish a difference in response to younger patients.

In clinical studies of eltrombopag and fostamatinib, no overall differences in effectiveness were observed in patients ≥ 65 years of age compared to younger patients.

Romiplostim dose adjustment in the elderly may be needed due to increased prevalence of hepatic, renal, and cardiac impairment. Elderly patients may also have an increased number of concomitant diseases and take multiple medications which can increase the risk for adverse reactions.

**Pregnancy**

There is insufficient data on use of avatrombopag, eltrombopag, and lusutrombopag in pregnant women to inform of a drug-associated risk to the fetus; however, all were shown to cause fetal harm in animal studies at doses substantially higher than human doses. Pregnant women should be advised of the potential risk of treatment with these agents.

While there are no available data of fostamatinib use in pregnancy, based on findings in animal studies and the mechanism of action, use during pregnancy may cause harm to the fetus. Pregnancy status should be verified prior to starting fostamatinib in females of reproductive potential.

Romiplostim (Nplate) is Pregnancy Category C. There are no adequate and well-controlled studies of romiplostim (Nplate) in pregnant women. A pregnancy registry has been established to collect information about the effects of romiplostim use during pregnancy. Physicians are asked to register
pregnant patients, or pregnant women may enroll themselves in the romiplostim pregnancy registry by calling 1-800-77-AMGEN (1-800-772-6436).

**Hepatic Impairment**

The initial dose of eltrombopag should be reduced when treating patients with chronic ITP or severe aplastic anemia who also have hepatic impairment.

No dosage adjustments are recommended for avatrombopag, fostamatinib, or lusutrombopag in patients with hepatic impairment.

No clinical studies have been conducted with romiplostim in patients with hepatic impairment.

**Renal Impairment**

No dosage adjustments are recommended for avatrombopag, fostamatinib, or lusutrombopag in patients with renal impairment.

No clinical studies have been conducted with romiplostim in patients with renal impairment. The effect of renal impairment on unbound (active) eltrombopag exposure has not been assessed.

**Race**

A reduction in the initial eltrombopag dose may be needed for patients of Asian (Chinese, Japanese, Taiwanese, Korean) ancestry and patients who are Asian with hepatic impairment.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Titration and/or Dosage timing</th>
<th>Availability</th>
</tr>
</thead>
</table>
| avatrombopag       | For patients with a platelet count of < 40 × 10⁹/L: 60 mg dose (3 tablets) orally once daily for 5 consecutive days  
                      For patients with a platelet count of 40 × 10⁹/L to < 50 × 10⁹/L: 40 mg (2 tablets) orally once daily for 5 consecutive days | Begin treatment 10 to 13 days prior to the scheduled procedure  
                      The procedure should occur 5 to 8 days following the last dose of avatrombopag       | 20 mg tablet     |
| eltrombopag         | ITP patients ≥ 6 years of age: 50 mg orally once daily  
                      ▪ For patients of Asian descent or with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily  
                      ▪ For patients of Asian descent and hepatic impairment (Child Pugh A, B, C): initial dose of 12.5 mg once daily may be considered  
                      patients 1-5 years of age: 25 mg orally once daily  
                      Chronic HCV-associated thrombocytopenia: 25 mg orally once daily  
                      Aplastic Anemia: 50 mg orally once daily  
                      ▪ For patients of Asian descent or with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily | Use the lowest dose to achieve and maintain platelet count ≥ 50 × 10⁹/L as needed to reduce the risk for bleeding  
                      If platelet > 400 × 10⁹/L, stop eltrombopag until platelet < 150 × 10⁹/L; reinitiate at a 25 mg dose reduction (or at 12.5 mg if the patient was already on 25 mg daily)  
                      Discontinue if platelet count is > 400 × 10⁹/L after 2 weeks of treatment using the lowest dose  
                      ITP: Increase or decrease the daily dose by 25 mg  
                      For patient taking 25 mg once daily increase or decrease the daily dose by 12.5 mg  
                      Do not exceed a dose of 75 mg daily  
                      Discontinue if platelet count does not increase to a sufficient level to avoid clinically important bleeding after 4 weeks of using 75 mg daily  
                      Chronic HCV-associated thrombocytopenia: Adjust dose in 25 mg increments every 2 weeks to achieve target platelet count necessary to initiate antiviral therapy  
                      Do not exceed 100 mg daily  
                      Discontinue eltrombopag when antiviral therapy is stopped  
                      Aplastic Anemia: Adjust dose in 50 mg increments every 2 weeks as needed to achieve platelet count ≥ 50 × 10⁹/L  
                      Do not exceed 150 mg daily  
                      May reduce dose by 50% in patients who attain transfusion independence for ≥ 8 weeks; if platelet level remains stable after 8 weeks after dose reduction, then discontinue eltrombopag and monitor platelet count  
                      Reinitiate at the previous effective dose for platelets < 30 × 10⁹/L or absolute neutrophil count (ANC) < 0.5 × 10⁹/L  
                      Discontinue if hematologic response is not seen within 16 weeks of initiating therapy | 12.5 mg, 25 mg, 50 mg, 75 mg tablets |
### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Titration and/or Dosage timing</th>
<th>Availability</th>
</tr>
</thead>
</table>
| fostamatinib (Tavalisse)   | Initial dose is 100 mg orally twice daily                                      | After 1 month, increase to 150 mg twice daily if platelet count is < $5 \times 10^9$/L  
Use the lowest dose to achieve and maintain platelet count ≥ $50 \times 10^9$/L  
Dosage should be reduced interrupted, or discontinued based on tolerability; a dose-reduction schedule provided in the product label  
Discontinue after 12 weeks if platelet count is not adequate to avoid clinically important bleeding | 100 mg, 150 mg tablets |
| lusutrombopag (Mulpleta)   | 3 mg orally once daily for 7 days                                              | Begin treatment 8 to 14 days prior to the scheduled procedure  
The procedure should occur 2 to 8 days following the last dose of lusutrombopag                                                                                                                                              | 3 mg tablet          |
| romiplostim (Nplate)       | 1 mcg/kg (based on actual body weight) weekly given by subcutaneous injection  
Syringes used for injection should have 0.01 mL graduations | Adjust the weekly dose by increments of 1 mcg/kg until the patient achieves a platelet count ≥ $50 \times 10^9$/L as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg; median dose is 2 mcg/kg weekly; do not dose if platelet count > $400 \times 10^9$/L  
Discontinue if platelet count does not increase after 4 weeks at the maximum dose of 10 mcg/kg; avoid shaking single-use vial during reconstitution, and protect from light  
Administer prepared solution within 24 hours using a syringe with 0.01 mL graduations | 250 mcg, 500 mcg vial |

Avatrombopag has not been studied other than as a single 5-day once daily dosing regimen. Lusutrombopag has only been studied as a single 7-day regimen.

Fostamatinib and lusutrombopag can be taken without regard to food. Avatrombopag should be taken with food.

Eltrombopag should be taken on an empty stomach given 1 hour before or 2 hours after a meal. Take ≥ 2 hours before or 4 hours after other medications, calcium-rich foods, or mineral supplements (calcium, iron, aluminum, magnesium, selenium, zinc).

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

Patients who have hepatic impairment (Child-Pugh Class A, B, C) may need a reduction in the initial dose of eltrombopag and close monitoring thereafter is warranted. After induction of eltrombopag therapy or an eltrombopag dose increase, prescribers should wait 3 weeks before any further increases in eltrombopag dose.
Monitoring

To ensure an adequate increase in platelet count, obtain a platelet count before treatment with avatrombopag on the day of a procedure. Similarly, obtain a platelet count prior to initiation of lusutrombopag therapy and not more than 2 days before the procedure.

With eltrombopag, typically platelet counts increase or decrease within 1 and 2 weeks of starting and stopping therapy, respectively. For eltrombopag, monitor CBC, including platelets, weekly during the dose adjustment phase of therapy with eltrombopag and then monthly following establishment of a stable dose. CBCs should be monitored prior to initiation of therapy, throughout therapy, and following discontinuation (weekly for ≥ 4 weeks) of eltrombopag. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and then monthly once a stable dose has been established. Fractionation should be performed if the patient’s bilirubin is elevated. If abnormal levels are detected, the test should be repeated within 3 to 5 days. Serum liver tests should be performed weekly if abnormalities are confirmed until the abnormalities resolve, stabilize, or baseline levels return. Discontinue eltrombopag if ALT levels increase to > 3 times the upper limit of normal (ULN) and are progressive, persistent for > 4 weeks, have increased direct bilirubin, include clinical symptoms of liver injury, or if there is evidence for hepatic decompensation. Hepatotoxicity risks versus benefits must be considered when reinitiating eltrombopag treatment. Weekly serum liver tests should be performed and if test abnormalities continue, worsen, or reoccur, eltrombopag should be permanently discontinued.

Discontinuation of eltrombopag and romiplostim may result in worse thrombocytopenia than was present prior to therapy. Monitor weekly CBCs, including platelet counts, for ≥ 4 weeks after discontinuation of eltrombopag or for ≥ 2 weeks following discontinuation of romiplostim.

For fostamatinib, after obtaining baseline assessments, monitor CBC monthly until a stable platelet count ≥ 50 × 10^9/L is achieved. Bilirubin, ALT, and AST should be monitored monthly. Monitor blood pressure every 2 weeks; if stable, may monitor monthly.

For romiplostim, monitor CBCs, including platelet counts and peripheral blood smears, prior to initiation of romiplostim. During romiplostim therapy, assess CBCs, including platelet count and peripheral blood smears weekly until a stable platelet count (≥ 50 × 10^9/L for ≥ 4 weeks without dose adjustment) has been achieved. CBCs, including platelet counts and peripheral blood smears, should be accessed monthly thereafter. In addition, CBCs, including platelet counts, should be performed weekly for ≥ 2 weeks following discontinuation of romiplostim therapy. Hyporesponsiveness or platelet response maintenance failure with romiplostim should prompt a search for causative factors, including neutralizing antibodies to romiplostim or bone marrow fibrosis. Blood samples can be submitted to Amgen (1-800-772-6436) in order to detect antibody formation. Amgen will assay the samples provided to identify antibodies to romiplostim and thrombopoietin. If platelet counts do not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of romiplostim therapy at the maximum weekly dose of 10 mcg/kg, discontinue therapy.
CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of ≥ 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

avatrombopag (Doptelet) versus placebo

Avatrombopag was evaluated for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo an elective invasive procedure with anticipated need for a platelet transfusion for procedure-related bleeding in 2 multicenter, randomized, double-blind, placebo-controlled trials, ADAPT-1 (n=231) and ADAPT-2 (n=204). In both trials, patients were stratified based on baseline platelet count (cohort-1, < 40 x 10^9/L; cohort-2, 40 x 10^9/L to < 50 x 10^9/L). Patients were then randomized (2:1) to receive 5 daily doses of avatrombopag or placebo; patients in cohort-1 received avatrombopag 60 mg or placebo, while patients in cohort-2 received avatrombopag 40 mg or placebo. Procedures were scheduled 5 to 8 days following the last dose of avatrombopag. The primary efficacy endpoint was the response rate, defined as the proportion of patients who did not require a platelet transfusion or rescue procedure for bleeding following randomization and within 7 days following the procedure. In cohort-1 within ADAPT-1, the response rate was 66% with avatrombopag compared to 23% with placebo (95% confidence interval [CI], 27 to 58; p<0.0001). In cohort-2 within ADAPT-1, the response rate was 88% with avatrombopag compared to 38% with placebo (95% CI, 32 to 68; p<0.0001). In ADAPT-2 cohort-1, the response rate was 69% with avatrombopag compared to 35% with placebo (95% CI, 16 to 52; p=0.0006). In cohort-2 within ADAPT-2, the response rate was 88% with avatrombopag compared to 33% with placebo (95% CI, 37 to 73; p<0.0001).

eltrombopag (Promacta) versus placebo for ITP

In a phase 3, randomized, multicenter, double-blind, placebo-controlled study, the efficacy, safety, and tolerability of eltrombopag 50 mg daily to 75 mg daily over 6 weeks were evaluated in 114 patients with chronic ITP. The patients had platelet counts < 30 x 10^9/L, and 1 or more previous ITP treatments. Standard treatment was continued. Initially patients were randomized to eltrombopag 50 mg daily or placebo. After 3 weeks, patients with platelet counts < 50 x 10^9/L could increase to eltrombopag 75 mg daily. Response was defined as the percentage of patients achieving platelet counts ≥ 50 x 10^9/L at day 43; 59% of eltrombopag-treated patients and 16% of placebo-treated patients achieved response (odds ratio 9.61; 95% CI, 3.31 to 27.86; p<0.0001). Median platelet count was 18 x 10^9/L in the placebo group and 69 x 10^9/L in the eltrombopag group. Response to
eltrombopag compared with placebo was not affected by predefined study stratification variables (baseline platelet counts, concomitant ITP drugs, and splenectomy status) or by the number of previous ITP treatments. Dose increase to eltrombopag 75 mg daily occurred in 34 out of 73 patients; 10 of the 34 patients had a positive response to eltrombopag treatment. Platelet counts returned to baseline values within 2 weeks after treatment discontinuation. Eltrombopag-treated patients had less bleeding during the study than placebo-treated patients (OR 0.49; 95% CI, 0.26 to 0.89; p=0.021.)

A randomized, double-blind, placebo-controlled study enrolled 118 patients with chronic ITP among placebo or 1 of 3 dose regimens of eltrombopag, 30 mg, 50 mg, or 75 mg each administered daily for 6 weeks. Patients had baseline platelet counts of < 30 × 10^9/L and had relapsed or were refractory to at least one standard ITP treatment. Primary endpoint was a platelet count of ≥ 50 × 10^9/L on day 43. The primary endpoint was achieved in 2%, 70%, and 81% of the eltrombopag-treated 30 mg, 50 mg, and 75 mg groups, respectively, compared to 11% of the placebo-treated group (p<0.001). The platelet count response to eltrombopag was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected 1 week following initiation of eltrombopag with the maximum response observed after 2 weeks of therapy. The median platelet counts on day 43 were 26 × 10^9/L in the 30 mg group, 128 × 10^9/L in the 50 mg group, and 183 × 10^9/L in the 75 mg group compared with 16 × 10^9/L in the placebo group. Bleeding events during treatment occurred less often in the eltrombopag 50 mg and 75 mg groups.

The RAISE study, a phase 3, randomized, double-blind, placebo-controlled clinical trial, enrolled 197 adults with previously treated ITP of > 6 months duration who had baseline platelet counts lower than 30 × 10^9/L. The study evaluated local standard of care plus eltrombopag 50 mg or placebo once daily for 6 months. Stratification of patients included baseline platelet count (≤ 15 × 10^9/L), use of treatment for immune thrombocytopenia, and splenectomy status. Eltrombopag dose modifications were made based on platelet response. Treatment response was defined as a platelet count of 50 to 400 × 10^9/L and occurred in 79% of patients receiving eltrombopag compared to 28% of patients in the placebo group. The percentage of patients receiving additional treatment was 59% in the eltrombopag-treated group and 32% in the placebo-treated group. Rescue medication was required in 18% of patients on eltrombopag and 40% of patients receiving placebo (p=0.001). Two percent of patients in the eltrombopag group had a thromboembolic event compared to none receiving placebo. Elevations in ALT were reported in 7% and 3% of patients receiving eltrombopag and placebo, respectively. Total bilirubin was reported in 4% of the eltrombopag group and none of the placebo group. Bleeding events were reported in 7% of the patients taking placebo compared to < 1% of the eltrombopag group. The study was supported by the manufacturer of eltrombopag.

**eltrombopag (Promacta) versus placebo in pediatrics for ITP**

The PETIT2 study, a 2-part, multicenter, placebo-controlled study, evaluated eltrombopag in 92 pediatric patients aged 1 to 17 years with chronic ITP and platelet counts < 30 × 10^9/L. Patients were stratified by age: 12 to 17 years, 6 to 11 years, and 1 to 5 years. In the double-blind phase, patients were randomized (2:1) to eltrombopag or placebo for the 13 weeks. Initial doses for patients aged 6 to 17 years weight-based and ranged from 50 mg/day and 25 mg/day, depending on ethnic origin. Starting dose for patients aged 1 to 5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for Asian patients. Patients who completed the double-blind period entered a 24-week, open-label treatment period in which all patients received eltrombopag at either their established dose or the starting dose, if they were previously on placebo. The primary outcome of the proportion of patients achieving platelet
counts of ≥ 50 × 10⁹/L without rescue therapy for ≥ 6 weeks of the 8-week double-blind period was met by 40% of eltrombopag-treated and 3% of placebo-treated patients (odds ratio, 18; 95% CI, 2.3 to 140.9; P=0.0004). Responses were similar in all cohorts. In addition, 37% of patients who received eltrombopag experienced WHO grades 1 to 4 bleeding at the end of the double-blind period compared to 55% who received placebo. During the 24-week open-label treatment period, 80% patients achieved platelet counts of ≥ 50 × 10⁹/L at least once.

**Eltrombopag (Promacta) versus placebo for chronic HCV-related thrombocytopenia**

Two randomized, placebo-controlled trials were conducted to evaluate safety and efficacy of eltrombopag for treatment of thrombocytopenia in adults with chronic hepatitis C receiving an antiviral regimen of either peginterferon alfa-2a (n=715) or peginterferon alfa-2b (n=805) in combination with ribavirin. Each study used a 2-phase method consisting of an open-label, pre-antiviral phase and a randomized, antiviral treatment phase. During the pre-antiviral phase of the study, eltrombopag was administered to patients with a platelet count of < 75 × 10⁹/L at an initial dose of 25 mg once daily for 2 weeks and then titrated to achieve a platelet count of ≥ 90 × 10⁹/L. If target platelet counts were achieved, patients were randomized to either eltrombopag or placebo for the antiviral phase of the study. The primary endpoint for both trials was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of the antiviral regimen. In both trials, a significantly greater number of patients treated with eltrombopag achieved SVR than those treated with placebo (P<0.05, 23 versus 14% for those receiving peginterferon 2-a and 19% versus 13% for patients peginterferon 2-b).

**Fostamatinib (Tavalisse) versus placebo**

The safety and efficacy of fostamatinib in chronic ITP was studied in 2 double-blind, randomized, placebo-controlled studies referred to as FIT-1 and FIT-2 that were identical in design. Patients (n=150) with persistent or chronic ITP, who had an insufficient response to previous treatment were enrolled in the 2 trials. Patients were randomized 2:1 to receive either fostamatinib or placebo for 24 weeks. Randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia. At baseline, the median platelet count was 16 × 10⁹/L, and 47% of patients were on stable ITP therapy. Patients initially received fostamatinib at 100 mg twice daily (or matching placebo). At week 4 or later, the dose escalated up to 150 mg twice daily (or matching placebo), based on platelet count and tolerability. Stable concurrent ITP therapy, including glucocorticoids (< 20 mg prednisone equivalent per day), azathioprine, or danazol was allowed, and rescue therapy (e.g., increased dosing of concomitant ITP therapy, immunoglobulin therapy, anti-D, steroids, and platelet infusion) was permitted, if necessary. The study outcome measure was stable platelet response defined as a platelet count of ≥ 50 × 10⁹/L on ≥ 4 of the 6 visits between weeks 14 to 24. In the FIT-1 study, 18% of fostamatinib patients versus 0% of placebo patients (P=0.03) achieved the study outcome. In the FIT-2 study, 16% of fostamatinib patients versus 4% of placebo patients achieved the study outcome, which was not statistically significant. Patients who did not respond to treatment after 12 weeks and patients who completed the 24-week study, were eligible to enroll in the FIT-3 open-label extension study (n=123 patients). Patients who were considered responders in the original study, continued their current trial dose and regimen at rollover; patients were non-responders (platelet < 50 × 10⁹/L) received fostamatinib 100 mg twice daily. Stable response in FIT-3 was defined as a patient initially achieving the target platelet count and then not having 2 visits (≥ 4 weeks apart) with a platelet...
count < 50 × 10⁹/L, without an intervening visit with a platelet count of ≥ 50 × 10⁹/L (unrelated to rescue therapy), within a period of 12 weeks. Of the 123 subjects, 61 (50%) discontinued the study early. Among patients who achieved stable response in FIT-1, FIT-2, and FIT-3, 18 patients maintained the platelet count of ≥ 50 × 10⁹/L for ≥ 12 months.

**lusutrombopag (Mulpleta) versus placebo**

The efficacy of lusutrombopag for the treatment of thrombocytopenia in adults with CLD who were scheduled to undergo a procedure was established in 2 randomized, double-blind, placebo-controlled trials, L-PLUS 1 (n=97) and L-PLUS 2 (n=215). In both trials, patients were stratified by liver ablation/coagulation or other procedures and baseline platelet count and were then randomized 1:1 to either lusutrombopag 3 mg or placebo once daily for up to 7 days. The primary efficacy outcome of L-PLUS 1 was the proportion of patients who did not require a platelet transfusion prior to the procedure. The primary efficacy outcome of L-PLUS 2 was the proportion of patients who did not require a platelet transfusion or rescue procedure for bleeding (e.g., platelet preparations, other blood preparations, including red blood cells [RBC] and plasma, volume expanders) following randomization and within 7 days following the procedure. A platelet transfusion was required if the platelet count was < 50 × 10⁹/L. Those who had a platelet count of ≥ 50 × 10⁹/L with an increase of ≥ 20 × 10⁹/L from baseline were considered responders. In L-PLUS 1, the proportion of patients not requiring platelet transfusion prior to the procedure was 78% and 13% in the lusutrombopag and placebo groups, respectively (difference, 64%; 95% confidence interval CI, 49 to 79; p<0.0001). The proportion of patients considered responders was 76% in the lusutrombopag group and 6% in the placebo group (difference, 68%; 95% CI, 54 to 82; p<0.0001). In L-PLUS 2, the proportion of patients not requiring platelet transfusion prior to the procedure or rescue therapy for bleeding from randomization through 7 days after invasive procedure was 65% and 29% in the lusutrombopag and placebo groups, respectively (difference, 37%; 95% CI, 25 to 49; p<0.0001). The proportion of patients considered responders was 65% in the lusutrombopag group and 13% in the placebo group (difference, 52%; 95% CI, 41 to 62; p<0.0001). The median (interquartile range [IQR]) duration of platelet count increase to ≥ 50 × 10⁹/L in patients without platelet transfusion was 22 days (IQR, 17 to 27) for patients treated with lusutrombopag and 1.8 days (IQR, 0 to 8.3) in placebo-treated patients in L-PLUS 1. The median (IQR) duration of platelet count increase to ≥ 50 × 10⁹/L in patients without platelet transfusion was 19 days (IQR, 13 to 28) for patients treated with lusutrombopag and 0 days (IQR, 0 to 5) in placebo-treated patients in L-PLUS 2.

**romiplostim (Nplate) versus placebo**

In 2 parallel studies, romiplostim was assessed for efficacy in the treatment of chronic ITP among splenectomized and non-splenectomized patients. A total of 63 splenectomized and 62 non-splenectomized patients with ITP and a mean of 3 platelet counts 30 × 10⁹/L or less were randomly assigned to romiplostim given subcutaneously (n=42 in splenectomized study and n=41 in non-splenectomized study) or placebo (n=21 in both studies) every week for 24 weeks. Romiplostim was initiated at 1 mcg/kg per week, and doses of romiplostim were adjusted to maintain platelet counts of 50 × 10⁹/L to 200 × 10⁹/L. Prior ITP treatments in both study groups included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (e.g., corticosteroids, IVIG, platelet transfusions,
and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage. The primary endpoints were measured by a durable platelet response (platelet count ≥ 50 × 10^9/L during 6 or more of the last 8 weeks of treatment) and safety data. Response was achieved by 38% of splenectomized patients given romiplostim versus none of 21 given placebo (difference in proportion of patients responding 38%, 95% CI; 23.4 to 52.8; p=0.0013), and by 61% of non-splenectomized patients given romiplostim versus 5% given placebo (difference in proportion of patients responding 56%; 95% CI, 38.7 to 73.7; p<0.0001). The overall platelet response rate (either durable or transient platelet response) was noted in 88% of non-splenectomized and 79% of splenectomized patients given romiplostim compared with 14% of non-splenectomized and no splenectomized patients given placebo (p<0.0001). Patients given romiplostim achieved platelet counts of > 50 × 10^9/L on a mean of 13.8 weeks (mean 12.3 weeks in splenectomized group versus 15.2 weeks in non-splenectomized group) compared with 0.8 weeks for those given placebo (0.2 weeks versus 1.3 weeks). Concurrent therapy was reduced by 25% or discontinued in 87% of patients given romiplostim (12/12 splenectomized and 8/11 non-splenectomized patients) compared with 38% of those given placebo. Adverse events were similar between groups. Antibodies against romiplostim or thrombopoietin were not detected. Moderate or greater severity bleeding events in the phase 3 trials were more common in the patients treated with placebo (34%) compared to patients treated with romiplostim (15%; p=0.018).72

Patients who had participated in either of the 2 studies were withdrawn from study medications.73 If platelet counts subsequently decreased to 50 ×10^9/L or less, the patients were allowed to receive romiplostim in an open-label extension study with weekly dosing based on platelet counts. Following romiplostim discontinuation in the 2 studies, 7 patients maintained platelet counts of ≥ 50 × 10^9/L. A total of 142 patients were enrolled. Patients previously treated with romiplostim received the same starting dose as the final dose given in the previous study, while those in the placebo-arm of the previous study were started on romiplostim 1 mcg/kg. Platelet counts were increased and sustained for up to 156 weeks (median treatment duration of 65 weeks). Overall, 87% of patients reached a platelet count of ≥ 50×10^9/L. Sixty-three percent of patients received romiplostim by self-administration. Serious treatment-related adverse effects and severe bleeding events were each reported in 9% of patients. In the long-term extension study, the incidence of bleeding adverse events of moderate or greater severity decreased from 23% of patients in the first 24 weeks to 12% after 24-48 weeks, remaining ≤ 6% thereafter.74

romiplostim (Nplate) versus standard care

In a randomized, open-label, 52-week, phase 3 study, romiplostim and standard care were compared in 234 adult patients with immune thrombocytopenia who had not undergone splenectomy.75 Primary outcome parameters were treatment failure and splenectomy. Secondary endpoints included the rate of a platelet response (a platelet count > 50 × 10^9/L at any scheduled visit), safety outcomes, and the quality of life. Patients receiving romiplostim had a significantly lower incidence of treatment failure (11%) than those receiving the standard of care (30%, p<0.001; odds ratio with romiplostim, 0.31; 95% CI, 0.15 to 0.61). Splenectomy also was performed less frequently in patients receiving romiplostim (9%) than in those receiving the standard of care (36%, p<0.001; odds ratio, 0.17; 95% CI, 0.08 to 0.35). For secondary endpoints, the rate of platelet response was higher with romiplostim compared to the standard care group (95% CI, 2 to 2.6; p<0.001). Lower rate of bleeding events and fewer blood transfusions were reported in the romiplostim group compared to the standard care group. Serious
adverse events were reported in 23% and 37% of the romiplostim and standard care groups, respectively.

META-ANALYSES

The Cochrane group performed a systematic review of the treatment of chronic ITP to determine the efficacy and safety of the thrombopoietin receptor agonists. Databases searched included Medline, EMBASE, and the Cochrane Central Register of Controlled trials to identify all randomized trials in ITP. Randomized controlled trials were included if the studies evaluated romiplostim or eltrombopag alone or in combination with other drugs, compared to placebo, or splenectomy. Six trials were identified with 808 patients. Five studies compared active treatment to placebo, and one study compared romiplostim to standard of care such as glucocorticoids, anti-D immune globulin, IVIG, rituximab, azathioprine, and others. Overall survival was not studied in these studies. Improvement in significant bleeding events did not reveal any significant differences between the thrombopoietin receptor agonists and the control group (versus placebo risk ratio 0.48; 95% CI, 0.20 to 1.15; versus SOC risk ratio, 0.49, 95% CI, 0.15 to 1.63). Overall platelet response was statistically improved with romiplostim and eltrombopag compared to placebo and standard of care (versus placebo RR 4.06, 95% CI 2.93 to 5.63; versus standard of care, RR 1.81, 95% CI 1.37 to 2.37), complete response (versus placebo RR 9.29, 95% CI 2.32 to 37.15) and durable response (versus placebo RR 14.16, 95% CI 2.91 to 69.01). Overall bleeding events were significantly reduced when compared to placebo (RR 0.78, 95% CI, 0.68 to 0.89), but not when compared to standard of care (RR 0.97, 95% CI, 0.75 to 1.26). Authors concluded that there was currently no evidence to support that thrombopoietin receptor agonists are effective in chronic ITP. Compared to placebo or standard of care, romiplostim and eltrombopag significantly increased platelet response, but there was no evidence that bleeding events were improved.

SUMMARY

Treatment options for ITP include corticosteroids, IVIG, anti-D immunoglobulin, splenectomy, and thrombopoietin receptor agonists. The spleen tyrosine kinase inhibitor, fostamatinib (Tavalisse), thrombopoietin receptor agonist (TBO-RA), eltrombopag (Promacta), and recombinant thrombopoiesis-stimulating Fc-peptide fusion protein, romiplostim (Nplate), are indicated for the treatment of thrombocytopenia in patients with chronic ITP who have failed to achieve an adequate response to corticosteroids, immunoglobulins, or splenectomy. These agents should only be used in patients with ITP who are at risk of bleeding, and should not be used for the treatment of thrombocytopenia due to causes other than chronic ITP (e.g., chemotherapy, myelodysplasia). Romiplostim is administered as a weekly subcutaneous injection, eltrombopag is an oral tablet dosed once daily, and fostamatinib is an oral tablet dosed twice daily. All 3 agents are indicated in adults; eltrombopag is also approved for use in patients as young as 1 year for ITP. Eltrombopag is also indicated to treat severe aplastic anemia and thrombocytopenia associated with chronic HCV interferon-based therapy. It carries a boxed warning regarding the increased risk for hepatic decompensation and death when used in combination with interferon and ribavirin.

The TBO-RAs, avatrombopag and lusutrombopag, are indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. Both are once-daily oral regimens, taken for 5 and 7 consecutive days, respectively.
The TPO-RAs and romiplostim have been associated with thrombotic and thromboembolic complications, eltrombopag is associated with new or worsening cataracts, and eltrombopag and romiplostim carry the risk of bone marrow reticulin fiber deposits. In addition, fostamatinib, eltrombopag, and romiplostim require frequent hematologic monitoring.

REFERENCES

1 Doptelet [package insert]. Durham, NC; Dova; May 2018.
3 Tavalisse [package insert]. South San Francisco, CA; Rigel; April 2018.
22 Doptelet [package insert]. Durham, NC; Dova; May 2018.
24 Tavalisse [package insert]. South San Francisco, CA; Rigel; April 2018.
27 Doptelet [package insert]. Durham, NC; Dova; May 2018.
29 Tavalisse [package insert]. South San Francisco, CA; Rigel; April 2018.
32 Doptelet [package insert]. Durham, NC; Dova; May 2018.
34 Tavalisse [package insert]. South San Francisco, CA; Rigel; April 2018.
Thrombopoiesis Stimulating Proteins Review – September 2018
Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2009-2018 Magellan Rx Management. All Rights Reserved.