


## PHARMACY / MEDICAL POLICY – 5.01.566

## Pharmacotherapy of Thrombocytopenia

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 24, 2025	5.01.556 Rituximab: Non-oncologic and Miscellaneous
Replaces:	Extracted from 5.01.550	8.01.503 Immune Globulin Therapy

Select a hyperlink below to be directed to that section.

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## Introduction

Thrombocytopenia means that a person has lower number of platelets than normal. Platelets are the cells in the blood that help blood to clot. Having a low number of platelets can cause bruises and increase the risk of bleeding. A number of disorders can cause low platelets, but one common cause occurs when the immune system attacks and destroys platelets. This is called chronic immune thrombocytopenia (ITP). Both adults and children can get an immune based thrombocytopenia. The treatment for ITP depends on a person's age, symptoms and how low the platelets are. This policy discusses the different types of treatment for thrombocytopenia with medications, and which medications need to be pre-approved by the health plan.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

## Policy Coverage Criteria

Click on the links below to be directed to the related medical necessity criteria:

[Chronic Immune Thrombocytopenia \(ITP\)](#)

[Severe Aplastic Anemia](#)

[Hepatitis C-associated  
Thrombocytopenia](#)

[Individuals with Hematopoietic  
Syndrome of Acute Radiation Syndrome](#)

[Chronic Liver Disease \(scheduled to  
undergo a procedure\)](#)

Agent	Medical Necessity
<b>Hepatitis C-associated Thrombocytopenia</b>	
<b>Thrombopoietic Agents</b> <ul style="list-style-type: none"><li>Alvaiz (eltrombopag choline) oral</li><li>Promacta (eltrombopag olamine) oral</li></ul>	<p><b>Alvaiz (eltrombopag choline) may be considered medically necessary as the first-line agent in the treatment of hepatitis C-associated thrombocytopenia and the daily dose does not exceed 72 mg per day.</b></p> <p><b>Promacta (eltrombopag olamine) may be considered medically necessary as the first-line agent in the treatment of hepatitis C-associated thrombocytopenia when the individual requires initiation and maintenance of interferon-based therapy and the daily dose does not exceed 100 mg per day.</b></p>
<b>Chronic Immune Thrombocytopenia (ITP)</b>	
<b>Thrombopoietic Agent</b> <ul style="list-style-type: none"><li>Doptelet (avatrombopag) oral</li></ul>	<p><b>Doptelet (avatrombopag) may be considered medically necessary for treatment of chronic immune thrombocytopenia (ITP) when all the following criteria are met:</b></p> <ul style="list-style-type: none"><li>The individual is aged 18 years or older</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>Meets one of the following:<ul style="list-style-type: none"><li>Has a platelet count of less than 30,000 µL</li></ul></li></ul> <p><b>OR</b></p> <ul style="list-style-type: none"><li>Has a platelet count of less than 50,000 µL and has an increased risk for bleeding</li></ul> <p><b>AND</b></p>



Agent	Medical Necessity
	<ul style="list-style-type: none"> <li>Has had an insufficient response to corticosteroids, immunoglobulins, rituximab, or splenectomy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The daily dose for Doptelet (avatrombopag) does not exceed 40 mg per day</li> </ul>
<p><b>Thrombopoietic Agents</b></p> <ul style="list-style-type: none"> <li><b>Alvaiz (eltrombopag choline)</b></li> <li><b>Promacta (eltrombopag olamine) oral</b></li> <li><b>Nplate (romiplostim) SC</b></li> </ul>	<p><b>Alvaiz (eltrombopag choline), Promacta (eltrombopag olamine), and Nplate (romiplostim) may be considered medically necessary for the treatment of chronic immune thrombocytopenia (ITP) when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual meets one of the following: <ul style="list-style-type: none"> <li>Has a platelet count of less than 30,000 <math>\mu</math>L</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>Has a platelet count of less than 50,000 <math>\mu</math>L and has an increased risk for bleeding</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has had an insufficient response to corticosteroids, immunoglobulins, rituximab, or splenectomy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The daily dose for Promacta (eltrombopag olamine) does not exceed 75 mg per day</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>The weekly dose for Nplate (romiplostim) does not exceed 10 mcg/kg</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>The daily dose of Alvaiz (eltrombopag choline) does not exceed 54 mg per day</li> </ul>
<p><b>Kinase Inhibitor</b></p> <ul style="list-style-type: none"> <li><b>Tavalisse (fostamatinib disodium hexahydrate) oral</b></li> </ul>	<p><b>Tavalisse (fostamatinib disodium hexahydrate) may be considered medically necessary for the treatment of chronic immune thrombocytopenia (ITP) when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Meets one of the following: <ul style="list-style-type: none"> <li>Has a platelet count of less than 30,000 <math>\mu</math>L</li> </ul> <p><b>OR</b></p> </li> </ul>



Agent	Medical Necessity
	<ul style="list-style-type: none"> <li>Has a platelet count of less than 50,000 <math>\mu</math>L and has an increased risk for bleeding</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has had an insufficient response to corticosteroids, immunoglobulins, rituximab, or splenectomy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has had an insufficient response to Promacta (eltrombopag olamine) or Nplate (romiplostim)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The daily dose for Tavalisse (fostamatinib disodium hexahydrate) does not exceed 300 mg per day</li> </ul> <p><b>Note:</b> Discontinue Tavalisse if platelet response is insufficient to prevent clinically important bleeding after 12 weeks.</p>
<b>Anti-CD20</b> <ul style="list-style-type: none"> <li>Rituxan (rituximab) IV</li> <li>Ruxience (rituximab-pvvr) IV</li> <li>Truxima (rituximab-abbs) IV</li> </ul>	<p><b>Rituximab is subject to review for site of service administration.</b></p> <p><b>See policy 5.01.556 Rituximab: Non-oncologic and Miscellaneous Uses</b></p>
<b>Chronic Liver Disease (scheduled to undergo a procedure)</b>	
<b>Thrombopoietic Agents</b> <ul style="list-style-type: none"> <li>Doptelet (avatrombopag) oral</li> <li>Mulpleta (lusutrombopag) oral</li> </ul>	<p><b>Doptelet (avatrombopag) or Mulpleta (lusutrombopag) may be considered medically necessary as prophylactic treatment of individuals with chronic liver disease when:</b></p> <ul style="list-style-type: none"> <li>The individual has a platelet count of less than 50,000 <math>\mu</math>L</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Is scheduled to undergo an invasive procedure within the next 14 days</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Quantity dispensed does not exceed fifteen 20 mg tablets of Doptelet (avatrombopag) or seven 3 mg tablets of Mulpleta (lusutrombopag)</li> </ul> <p><b>Doptelet (avatrombopag) or Mulpleta (lusutrombopag) will be approved for one course of therapy per procedure, according to the above criteria.</b></p>
<b>Severe Aplastic Anemia</b>	



Agent	Medical Necessity
<b>Thrombopoietic Agents</b> <ul style="list-style-type: none"> <li>Alvaiz (eltrombopag choline)</li> <li>Promacta (eltrombopag olamine) oral</li> </ul>	<p><b>Alvaiz (eltrombopag choline) may be considered medically necessary as the first-line agent in the treatment of severe aplastic anemia when:</b></p> <ul style="list-style-type: none"> <li>The individual has had insufficient response to immunosuppressive therapy and the daily dose does not exceed 108 mg per day.</li> </ul> <p><b>Promacta (eltrombopag olamine) may be considered medically necessary as the first-line agent in the treatment of severe aplastic anemia when:</b></p> <ul style="list-style-type: none"> <li>The individual has had insufficient response to immunosuppressive therapy and the daily dose does not exceed 150 mg per day.</li> </ul> <p><b>Promacta (eltrombopag olamine) may be considered medically necessary for the first-line treatment of severe aplastic anemia when all the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 2 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Promacta (eltrombopag olamine) is used in combination with standard immunosuppressive therapy</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>The daily dose does not exceed 150 mg per day.</li> </ul> <p><b>Note:</b> Examples of standard immunosuppressive therapy include horse antithymocyte globulin [ATG], rabbit ATG, cyclosporine, prednisone, and methylprednisolone</p>
<b>Individuals with Hematopoietic Syndrome of Acute Radiation Syndrome</b>	
<b>Thrombopoietic Agents</b> <ul style="list-style-type: none"> <li>Nplate (romiplostim) SC</li> </ul>	<p><b>Nplate (romiplostim) may be considered medically necessary in adults and in pediatric individuals (including term neonates) acutely exposed to myelosuppressive doses of radiation.</b></p>
<b>Chemotherapy-Induced Thrombocytopenia</b>	
<b>Thrombopoietic Agents</b> <ul style="list-style-type: none"> <li>Nplate (romiplostim) SC</li> </ul>	<p><b>Nplate (romiplostim) may be considered medically necessary for the treatment of chemotherapy-induced thrombocytopenia when all the following are met:</b></p>



Agent	Medical Necessity
	<ul style="list-style-type: none"> <li>The individual has experienced chemotherapy-induced thrombocytopenia for greater than or equal to 4 weeks</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has not responded to a reduction in the chemotherapy dose or frequency</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has a platelet count less than 100,000/<math>\mu</math>L</li> </ul>
<b>Congenital Thrombotic Thrombocytopenic Purpura</b>	
<b>Adzynma (ADAMTS13, recombinant-krhn)</b>	<p><b>Adzynma (ADAMTS13, recombinant-krhn) may be considered medically necessary for the treatment of congenital thrombotic thrombocytopenic purpura (cTTP) when all the following are met:</b></p> <ul style="list-style-type: none"> <li>The individual has been diagnosed with cTTP confirmed by molecular genetic testing</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has ADAMTS13 activity less than 10% as measured by the fluorescent resonance energy transfer-von Willebrand factor 73 (FRETs-VWF73) assay</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has not been diagnosed with immune-mediated thrombotic thrombocytopenia purpura (iTTP)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has had an inadequate response or contraindication to plasma transfusion therapy OR a documented allergy to plasma products</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>For prophylactic therapy, the dose is limited to 40 IU/kg once weekly</li> </ul>

Drug	Investigational
<b>As listed</b>	<p><b>The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</b></p> <p><b>The use of Adzynma (ADAMTS13, recombinant-krhn), Alvaiz (eltrombopag choline), Doptelet (avatrombopag), Mulpleta</b></p>

Drug	Investigational
	<p>(lusutrombopag), Promacta (eltrombopag olamine), and Tavalisse (fostamatinib disodium hexahydrate) are considered investigational for other indications, including but not limited to:</p> <ul style="list-style-type: none"> <li>Chemotherapy-induced thrombocytopenia</li> </ul> <p>All other uses of Nplate (romiplostim) are considered investigational.</p>

Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<p>Non-formulary exception reviews for drugs listed in this policy may be approved up to 12 months when medical necessity criteria specified above are met.</p> <p>All other reviews for drugs listed in this policy may be approved up to 3 months when medical necessity criteria specified above are met.</p>
<b>Re-authorization criteria</b>	<p>Non-formulary exception reviews for drugs listed in this policy may be approved up to 12 months if the drug-specific conditions are met, the individual has shown and continues to show clinical benefit (eg, platelet count meets goal), and individual has not had any clinically significant bleeds while on therapy.</p> <p>All other reviews for drugs listed in this policy may be approved up to 6 months if the drug-specific conditions are met, the individual has shown and continues to show clinical benefit (eg, platelet count meets goal), and individual has not had any clinically significant bleeds while on therapy.</p>

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

## Documentation Requirements

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

## Coding

Code	Description
<b>HCPCS</b>	
C9167	Injection, apadamtase alfa (Adzynma), 10 units (code terminated 07/01/24)
J2796	Injection, romiplostim (Nplate), 10 mcg (code terminated 01/01/25)
J2802	Injection, romiplostim (Nplate), 1 microgram (new code effective 01/01/25)
J7171	Injection, adams13, recombinant-krhn, (Adzynma) 10 iu (new code effective 07/01/24)

## Related Information

### Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

### Benefit Application

Alvaiz (eltrombopag choline), Doptelet (avatrombopag), Mulpleta (lusutrombopag), Promacta (eltrombopag olamine), and Tavalisse (fostamatinib disodium hexahydrate) are managed through the pharmacy benefit. Adzynma (ADAMTS13, recombinant-krhn) is managed through the medical benefit. Nplate (romiplostim) is managed through both the pharmacy and medical benefit.

## Evidence Review





The term “autoimmune disorders” covers a wide range of syndromes often involving damage to multiple organ systems. Since the advent of biologics and small molecule targeted therapies, a variety of pathways and specific points of intervention have been identified and drugs developed to modify the disease pathology. Since multiple diseases share common signaling pathways, it is not surprising that drugs and diseases often overlap, leading to the complex web of alternative therapies that are now available to physicians.

Chronic immune thrombocytopenia (ITP) is an autoimmune disorder characterized by destruction of normal platelets due to unknown stimulus and a resulting risk of severe bleeding complications. Recent update by International Working Group (IWG) consensus panel set the platelet count threshold as less than 100,000 per  $\mu\text{L}$ . The initiating event of ITP is unclear and various mechanisms of platelet destruction may be important. IgG autoantibodies on the platelet surface can cause platelet uptake and destruction by reticuloendothelial phagocytes. T-cell mediated cytotoxicity against megakaryocytes and platelets may cause thrombocytopenia. In addition to increased platelet destruction, the production of platelets is often decreased in ITP.

Adult ITP has an annual incidence of approximately two cases per 100,000. It is estimated in the United States there are 100 individuals with ITP per one million people or approximately 30,000 total and 15,000 with a chronic form of ITP assuming the population is 300 million. Adult ITP is more likely than childhood ITP to be chronic. Spontaneous remission occurs in more than 80% of cases in children but is uncommon in adults. As a result, evidence-based treatment guidelines differ between adults and children. For specific treatment recommendations in children with ITP, please refer to the ASH 2011 guideline “Section 1: ITP in children” or ASH 2019 guideline “Management of children with newly diagnosed ITP”. The incidence rate appears to increase with age, with the highest age-specific incidence in individuals older than 60 years of age. The female-to-male ratio of ITP individuals is bimodal, being 1.9 women for each man in ages less than 50 and 1.2:1 in ages 65 and older. There is no apparent prevalence difference between African Americans and whites. Intracranial hemorrhage represents the most serious complication of ITP. The mortality rate from hemorrhage is approximately 1% in children and 5% in adults. In individuals with severe thrombocytopenia, predicted five-year mortality rates from bleeding are significantly raised in individuals older than 60 years versus individuals younger than 40 years, 47.8% versus 2.2%, respectively.

Longer courses of corticosteroids may be preferred over shorter courses of corticosteroids or IVIg as first-line treatment. IVIg may be used in addition to corticosteroids when a more rapid increase in platelet count is required. Either IVIg or anti-D (in appropriate individuals) may be used as a first-line treatment if corticosteroid are contraindicated. The criteria for using



Intravenous Immune Globulin (IVIG) to treat ITP are addressed separately in another medical policy (see [Related Policies](#)). The use of rituximab and human thrombopoietin (TPO) agents are not recommended in the initial treatment of ITP. Rituximab may be considered for treatment of chronic adult ITP or in those who are unresponsive to or relapse after initial corticosteroid therapy or have failed splenectomy. FDA-approved agents are Nplate (romiplostim), Promacta (eltrombopag), Tavalisse (fostamatinib disodium hexahydrate), and Doptelet (avatrombopag). The optimal treatment for individuals requiring second-line therapy is uncertain. Guidelines and expert opinions have not reached consensus due to the lack of comparative clinical and economic data. This policy is based on ASH 2011 and ASH 2019 which are well-established evidence-based guidelines. Selection of a treatment option should take into consideration the individual patient's bleeding risk, activity level, likely side effects of treatment and individual preferences. This guideline and several other expert reviews support the use of rituximab as a second line treatment option for individuals with ITP who have failed at least one other therapy such as corticosteroids, IVIG, or splenectomy.

## **Efficacy of Promacta (eltrombopag)**

There are three published clinical trials evaluating the efficacy and safety of Promacta (eltrombopag) in chronic immune thrombocytopenia (ITP). A Phase II pivotal study showed that significantly more subjects treated with eltrombopag 50 mg (70%) and 75 mg (81%) responded to therapy compared to placebo (11%) ( $P < 0.001$ ). About one third of the subjects used concomitant ITP medications during the study, and one half of the subjects were splenectomized. Although it was noted that response was higher in those treated with concomitant medications, stratified results for these subgroups were not presented. Bleeding events were only considered as secondary endpoints, and the results showed that subjects treated with eltrombopag 30 mg and 50 mg showed fewer signs of bleeding than placebo, but subjects treated with eltrombopag 75 mg showed increased signs of bleeding.

Another Phase III pivotal trial showed that the primary endpoint of response, defined as subjects who had an increase in platelet counts to  $\geq 50,000/\mu\text{L}$  at week six, was reached in 58.9% of those treated with eltrombopag versus 16.2% of those receiving placebo ( $P < 0.001$ ). Additionally, this study showed that the odds of responding were significantly higher in the eltrombopag group versus the placebo group ( $P < 0.001$ ). Response to eltrombopag was not statistically significantly affected by concomitant treatment ( $P = 0.766$ ), prior splenectomy ( $P = 0.747$ ) or having baseline platelet counts below  $15,000/\mu\text{L}$  ( $P = 0.453$ ). Bleeding events were considered as a secondary endpoint and significantly fewer events took place in the



eltrombopag group versus placebo (39% and 60%, respectively;  $P = 0.029$ ), however the trial was not powered to detect such differences.

An ongoing, Phase III extension trial (EXTEND) evaluating the long-term efficacy of eltrombopag showed that 50% of enrolled subjects had a continuous response (platelet count  $\geq 50,000$ ) for more than four weeks, 35% for at least 10 weeks, and 24% for more than six months. At the one-year time point, only 7% of individuals still showed response. A summary of this study in the manufacturer's dossier states that 48% of individuals were able to discontinue or reduce concomitant ITP medications, and that bleeding events were significantly reduced for eltrombopag-treated individuals. Since data from this study is only available in post-hoc reviews, it is not yet possible to evaluate the validity or usefulness of these results.

## Efficacy of Nplate (romiplostim)

In the published RCT of Nplate (romiplostim) for the treatment of chronic immune thrombocytopenia (ITP), a statistically significant response was achieved by subjects treated with romiplostim (49%) compared to placebo (2%) ( $P < 0.0001$ ). Romiplostim also showed a statistically significant reduction in the dependence on rescue medication (21.7%) compared to placebo (59.5%) ( $P < 0.0001$ ). Limitations of this study include that all participants were allowed use of concurrent ITP medications, and the results were not stratified to demonstrate the effect of these medications on the results. Additionally, the primary endpoint of this study was to determine the platelet response of individuals to romiplostim, whereas bleeding events were a secondary endpoint. It would have been more clinically relevant if the study would have been specifically powered to determine the difference in bleeding events between romiplostim and placebo-treated subjects.

There is an ongoing, open-label extension study to evaluate the long-term safety and efficacy of romiplostim in subjects who had previously completed a romiplostim trial. The primary endpoint is platelet response, defined as a platelet count of  $\geq 50,000/\mu\text{L}$ . Throughout the study, 18 subjects never met the primary endpoint, but 10 of those still continued with the treatment. After a sharp increase in platelet counts during the first four weeks, platelet counts generally remained stable or gradually increased through week 144. The study reported platelet responses of 30% after the first dose and 51% after the third dose. Subjects that responded had a response during 67% of the weeks enrolled in the study. The results reported do not include any raw numbers, but are reported solely as percentages, except for the instance of those that showed a response at least once. This study lacks definitive information to demonstrate that a response to romiplostim once or continually will result in prevention of adverse events or improve mortality and morbidity.

No head-to-head trials have been conducted between eltrombopag or romiplostim and other agents used to treat chronic ITP, such as IVIg, anti-D, or rituximab. Five small uncontrolled studies were found reporting response rates generally in the 30-40% range. These are classified as case series and are considered Level C evidence. No head-to-head studies versus romiplostim, eltrombopag or IVIG were found.

## **Efficacy of Doptelet (avatrombopag)**

Avatrombopag was shown to be efficacious based on ADAPT-1 and -2 trials. Individuals were separated into high (40-50,000/ $\mu$ L) or low (<40,000/ $\mu$ L) baseline platelet count cohorts. In both cohort groups, avatrombopag was more effective in preventing use of platelet transfusions or rescue therapies for bleeding. The high baseline cohort (received avatrombopag 40 mg) in ADAPT-1 had 88.1% vs 38.2% when comparing efficacy of study drug versus placebo, and in ADAPT-2, 87.9% vs 33.3%, respectively. In the low baseline cohort (received avatrombopag 60 mg), the primary endpoint was reached in 65.6% vs 22.9% of individuals when comparing study drug and placebo in ADAPT-1, and in ADAPT-2, 68.6% vs 34.9%, respectively. Evidence was limited due to smaller sample sizes and no direct comparison to standard therapy (platelet transfusions).

Evidence for lusutrombopag efficacy is limited due to only two phase III trial, in which only abstracts were available at the time of review; complete results are not yet available. Nonetheless, 64.8% of individuals on lusutrombopag compared to 29.0% on placebo did not need platelet transfusions or rescue therapies for bleeding.

## **Safety of Promacta (eltrombopag), Doptelet (avatrombopag), Mulpleta (lusutrombopag) and Nplate (romiplostim)**

The evidence for the safety of eltrombopag and romiplostim is based on clinical studies, which are considered to be Level B evidence. Although eltrombopag and romiplostim have shown to have mostly mild side effects, rare but serious adverse reactions have been reported. The safety of eltrombopag and romiplostim seem to be similar, however some additional adverse events have occurred in individuals treated with one or the other medication.

Bone marrow reticulin formation and risk for bone marrow fibrosis have been associated with the use of eltrombopag and romiplostim. TPO-receptor agonists increase the risk for formation or progression of reticulin fiber deposition within bone marrow. Peripheral blood smears have



confirmed the presence of bone marrow reticulin formation in both the eltrombopag and romiplostim clinical trials. Prior to the initiation of these medications, peripheral blood smears must be obtained and examined to establish a baseline level of cellular abnormalities and obtained along with complete blood counts (CBCs) monthly after the initiation of either.

Worsened thrombocytopenia and increased risk of bleeding has been associated with the cessation of eltrombopag and romiplostim. Thrombocytopenia may be of greater severity than prior to initiation of either agent, which can increase the risk of bleeding. The increased risk of bleeding may be particularly apparent in individuals on anticoagulants or antiplatelet agents. Follow-up studies of both medications have indicated that the rebound effect is transient, but CBCs with platelets should be obtained weekly for at least two weeks following discontinuation.

Thrombotic/thromboembolic events may occur from excessive increases in platelet counts, associated with excessive doses of eltrombopag and romiplostim. To minimize this risk, these medications should not be administered to normalize platelet counts. Caution should be used when administering either medication to individuals with known risks for thromboembolism.

Development and progression of hematological malignancies have been observed in individuals treated with eltrombopag or romiplostim, due to the stimulation of the TPO-receptor on the surface of hematopoietic cells. This risk may be particularly important in myelodysplastic syndrome. These agents should not be used to treat any thrombocytopenia other than ITP.

Eltrombopag carries a Black Boxed Warning for hepatotoxicity. Hepatotoxicity was one of the most commonly reported severe adverse events in individuals treated with eltrombopag. Hepatotoxicity has not been reported in individuals treated with romiplostim, likely due to the lack of first pass metabolism because it is administered IV. Grade 4 liver abnormalities were reported in individuals treated with eltrombopag in randomized controlled trials (RCTs), whereas none were reported in individuals treated with placebo. ALT, AST, and bilirubin should be measured prior to the initiation of eltrombopag, every two weeks during dose titration, and monthly after a stable dose has been established. Abnormal tests should be repeated within three to five days, and if confirmed, serum liver tests should be monitored weekly until they resolve. Eltrombopag should be discontinued if ALT levels reach  $\geq$  three times baseline and are progressive, persistent for  $\geq$  four weeks, or are accompanied by increased direct bilirubin, clinical symptoms of liver injury or evidence for hepatic decompensation.

Cataracts have developed or worsened in some individuals treated with eltrombopag. Eltrombopag was shown to cause cataracts in pre-clinical trials of rodents. Ocular examinations should be performed prior to the initiation of eltrombopag, and individuals should be regularly monitored for signs and symptoms of cataracts during treatment.

A lack or loss of platelet response has been demonstrated in individuals treated with romiplostim. Individuals who are hyporesponsive or fail to respond should be evaluated for causative factors, including formation of neutralizing antibodies or bone marrow fibrosis. Blood samples should be submitted to Amgen for assay to determine antibody formation against romiplostim or TPO. Romiplostim should be stopped after four weeks on the highest dose (10 µg/kg) if sufficient platelet levels have not been achieved to avoid clinically important bleeding.

Adverse effects in avatrombopag appear to be pretty similar to placebo based on both ADAPT trials. Most side effects were mild to moderate in severity and consisted of pyrexia, abdominal pain, nausea, headache, fatigue, and peripheral edema. Lusutrombopag adverse effects included procedural pain and hypertension.

ADAPT trials and package insert provided a good idea of safety for avatrombopag, but data for safety was limited by availability of studies for lusutrombopag.

## **Adzynma (ADAMTS13, recombinant-krhn)**

The safety and effectiveness of Adzynma were demonstrated in a global study (NCT03393975) evaluating prophylactic and on-demand enzyme replacement therapy (ERT) with Adzynma compared to plasma-based therapies in individuals with cTTP. The clinical trial encompassed a two-period crossover study followed by a single arm continuation period. In the prophylactic treatment cohort two-period crossover study, 46 individuals with cTTP were randomized to receive 6 months of treatment with either Adzynma or plasma-based therapies (Period 1) and then crossed over to receive the other treatment for 6 months (Period 2). Efficacy was demonstrated based on the incidence of TTP events and TTP manifestations, as well as the incidence of the need for supplemental doses. Following Periods 1 and 2 of the pivotal study, all individuals were treated with Adzynma (Period 3). The efficacy of on-demand ERT was evaluated based on the proportion of acute TTP events responding to Adzynma in both the prophylactic and the on-demand cohorts throughout the duration of the study. A total of 35 individuals entered Period 3 of the study. No subacute TTP events were reported in individuals receiving Adzynma during Periods 1 and 2. In Period 3, two individuals receiving Adzynma prophylaxis had two subacute events, of which one was treated with four supplemental doses. Four individuals receiving plasma-based therapies had a total of five subacute TTP events in Periods 1 and 2.

Efficacy of Adzynma remained consistent throughout the study, including Period 3, and across all age groups. The efficacy of Adzynma for on-demand ERT was evaluated based on the proportion of acute TTP events responding to Adzynma in both the prophylactic and the on-

demand cohorts throughout the duration of the study. An acute TTP event responding to Adzynma was defined as a resolved TTP event when platelet count was  $\geq 150,000/\mu\text{L}$  or within 25% of baseline, whichever occurred first, and LDH was  $\leq 1.5 \times$  baseline or  $\leq 1.5 \times$  ULN, without requiring the use of another ADAMTS13-containing agent. Five adult individuals ( $\geq 18$  years of age) enrolled in the on-demand cohort and had a total of six acute TTP events. Of these five individuals, two individuals were randomized to receive on-demand treatment with Adzynma, and three individuals were randomized to receive plasma-based therapies. All six acute TTP events resolved after treatment with either Adzynma or plasma-based therapies. The most common side effects associated with Adzynma include headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting.

## 2017 Update

Dosage and quantity limits with specific age range of eltrombopag is updated.

## 2018 Update

Tavalisse (fostamatinib) criteria, dosage, and quantity limits were added to policy. Length of approval table was also added to policy which encompasses all drugs listed within this medical policy.

## 2019 Update

Reviewed prescribing information and conducted literature search for all drugs listed in policy. Updated Doptelet (avatrombopag) criteria to include coverage for chronic immune thrombocytopenia (ITP) indication. Updated description of condition from chronic immune (idiopathic) thrombocytopenia (ITP) and immune thrombocytopenia purpura (ITP) to chronic immune thrombocytopenia (ITP). Both the prescribing information and literature now consistency refer to condition as chronic immune thrombocytopenia (ITP). Removed a separate Dosage and Quantity Limits table and inserted the applicable quantity limits from table into the medical necessity criteria.



## 2020 Update

Reviewed prescribing information for all drugs listed in policy, the American Society of Hematology 2019 guidelines for immune thrombocytopenia, and information on UpToDate for Immune thrombocytopenia (ITP) in adults: Second-line and subsequent therapies. For second-line therapy in adults with ITP rituximab was added as a treatment option for ITP. Revised criteria after insufficient response to corticosteroids require the individual has had an insufficient response to an immune globulin (IVIg), rituximab, or splenectomy.

## 2021 Update

Reviewed prescribing information for all drugs listed in policy. Identified a new indication for Nplate (romiplostim) and added to the policy for the treatment of adults and in pediatric individuals (including term neonates) acutely exposed to myelosuppressive doses of radiation.

## 2022 Update

Reviewed prescribing information for all drugs listed in policy and information on UpToDate for Immune thrombocytopenia (ITP) in adults: Second-line and subsequent therapies. No new information was identified that would require a change to policies.

## 2023 Update

Reviewed prescribing information for all drugs listed in policy. Updated chronic immune thrombocytopenia criteria for Promacta (eltrombopag), Nplate (romiplostim), Doptelet (avatrombopag), and Tavalisse (fostamatinib disodium hexahydrate). Removed the step therapy requirement from the Doptelet criteria that individual has had an insufficient response to Promacta (eltrombopag) or Nplate (romiplostim) based on the formulary and guideline. Removed trade marks from the brand names for the process of standardization.

## 2024 Update

Reviewed prescribing information for all drugs listed in policy. Added coverage criteria for Alvaiz (eltrombopag choline). Added coverage criteria for Adzynma (ADAMTS13, recombinant-krhn)





for the treatment of certain individuals with congenital thrombotic thrombocytopenic purpura (cTTP). Updated Nplate (romiplostim) to include coverage criteria for chemotherapy-induced thrombocytopenia.

## 2025 Update

Reviewed prescribing information for all drugs listed in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

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## History

Date	Comments
07/01/16	New policy approved June 14, 2016. Add to Prescription Drug section. Policy information on drug treatment for miscellaneous autoimmune diseases extracted from 5.01.550. Medical necessity review criteria for site of service IV therapy added.
11/01/16	Interim Review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages.
07/01/17	Formatting update; added hyperlinks to Medical Necessity Criteria sections.



Date	Comments
10/01/17	Annual Review, approved September 21, 2017. Updated dosage and quantity limits with specific age range of eltrombopag.
08/01/18	Annual Review, approved July 13, 2018. Tavalisse™ (fostamatinib) criteria and dosage and quantity limits were added to policy. Length of approval table was also added to policy which encompasses all drugs listed within this medical policy. Removed HCPCS code J8499.
10/01/18	Interim Review, approved September 11, 2018. Updated to add criteria for avatrombopag and lusutrombopag, recently FDA-approved for chronic liver disease patients undergoing invasive procedures. Criteria approved by the P&T Committee 8/28/18. Removed HCPCS codes J3490 and J3590.
03/01/19	Interim Review, approved February 12, 2019. Updated criteria for Promacta (eltrombopag).
08/01/19	Annual Review, approved July 9, 2019. Updated criteria for Doptelet® (avatrombopag). Updated description of condition from chronic immune (idiopathic) thrombocytopenia (ITP) and immune thrombocytopenia purpura (ITP) to chronic immune thrombocytopenia (ITP).
01/01/20	Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification. Noted Ruxience (rituximab-pvvr) and Truxima (rituximab-abbs) along with Rituxan (rituximab).
11/01/20	Annual Review, approved October 22, 2020. Updated criteria for Promacta (eltrombopag), Nplate (romiplostim), Tavalisse (fostamatinib disodium hexahydrate), and Doptelet (avatrombopag) when used for the treatment of ITP adding rituximab as a second-line treatment option in addition to IVIg and splenectomy.
01/01/22	Annual Review, approved December 2, 2021. Added a new indication to Nplate (romiplostim) for the treatment of patients acutely exposed to myelosuppressive doses of radiation.
12/01/22	Annual Review, approved November 7, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. Updated chronic immune thrombocytopenia criteria for Promacta (eltrombopag), Nplate (romiplostim), Doptelet (avatrombopag), and Tavalisse (fostamatinib disodium hexahydrate).
09/01/23	Interim Review, approved August 8, 2023. Removed the step therapy requirement from the Doptelet criteria that individual has had an insufficient response to Promacta (eltrombopag) or Nplate (romiplostim) based on the formulary and guideline.
10/16/23	Formatting update. Moved the location of Doptelet within the policy criteria for clarity. Otherwise, policy statement unchanged.
05/01/24	Annual Review, approved April 9, 2024. Added coverage criteria for Alvaiz (eltrombopag choline). Added coverage criteria for Adzynma (ADAMTS13,



Date	Comments
	recombinant-krhn) for the treatment of certain individuals with congenital thrombotic thrombocytopenic purpura (cTTP). Updated Nplate (romiplostim) to include coverage criteria for chemotherapy-induced thrombocytopenia. Added C9167.
07/01/24	Coding update. Terminated HCPCS code C9167 and added HCPCS code J7171.
01/01/25	Coding update. HCPCS J2796 termed and replaced with HCPCS J2802.
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premiera All Rights Reserved.

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