

Drug Class Review: Thrombocytopenia

Date of Review: January 2019

End Date of Literature Search: 11/05/2018

Purpose for Class Review:

Treatments for thrombocytopenia are being reviewed for the first time, prompted by the recent approval of three new drugs; avatrombopag (Doptelet®), fostamatinib (Tavalisse™) and lusutrombopag (Mulpleta®).

Research Questions:

1. What is the evidence for efficacy and harms of thrombocytopenia treatments (avatrombopag, eltrombopag, lusutrombopag, fostamatinib, and romiplostim)?
2. Is there any comparative evidence for therapies for thrombocytopenia pertaining to important outcomes such as mortality, bleeding rates, and platelet transfusions?
3. Is there any comparative evidence based on the harms outcomes of thrombocytopenia treatments?
4. Are there subpopulations of patients for which specific thrombocytopenia therapies may be more effective or associated with less harm?

Conclusions:

- Three guidelines, six randomized clinical trials and five high-quality systematic reviews and meta-analyses met inclusion criteria for this review. There was insufficient direct comparative evidence between different therapies to treat thrombocytopenia. A majority of trials were small and of short duration.
- Guidelines recommend corticosteroids and intravenous immunoglobulin (IVIg) as first-line therapy for most adults with idiopathic thrombocytopenia (ITP). Thrombopoietin receptor agonists (TPOs) and the tyrosine kinase inhibitor, fostamatinib, are recommended as second-line treatments after failure of at least one other treatment.¹⁻³ Avatrombopag and lusutrombopag are only approved for short-term use before procedures in patients with chronic liver failure.
- There is insufficient evidence or low quality evidence to demonstrate an improvement in survival as a result of TPO therapy in patients with thrombocytopenia due to chronic bone marrow failure, chronic idiopathic thrombocytopenic purpura or myelodysplastic syndrome (MDS) based on three meta-analyses.⁴⁻⁶
- In patients with chronic ITP, TPOs (eltrombopag and romiplostim) were associated with similar rates of overall bleeding compared to standard of care (SOC) (e.g., glucocorticoids, anti-D immune globulin, intravenous immune globulin, rituximab, azathioprine, etc.) (relative risk [RR] 0.97; 95% confidence interval [CI] 0.75 to 1.26; P>0.05).⁴ There was moderate quality of evidence that overall bleeding rates were statistically lower with TPOs compared to placebo, with or without azacitidine, decitabine or lenalidomide, in patients with myelodysplastic syndrome, 70% vs. 71% (RR 0.92; 95% CI, 0.86 to 0.99). A clinical difference in overall bleeding is unlikely due to the small differences in rates.

- There is insufficient evidence for the use of TPOs for the treatment or prevention of thrombocytopenia in patients being treated with chemotherapy for solid tumors.⁷

Avatrombopag

- In adults with thrombocytopenia and chronic liver disease avatrombopag decreased the proportion of patients requiring platelet transfusions or rescue procedures for bleeding up to 7 days after a scheduled procedure, based on two small, industry funded trials (low strength of evidence)(**Table 2**).⁸
- Adverse events were similar between avatrombopag and placebo and serious adverse events were not significantly different.

Fostamatinib

- There is low quality evidence that fostamatinib is more effective than placebo at increasing platelets to a stable level, defined as platelets $\geq 50,000/\mu\text{L}$ in 4 or more of the 6 biweekly visits, in patients with chronic ITP over 24 weeks who were also taking other therapies for ITP; however 82% of patients even with fostamatinib were not able to obtain stable platelet counts (**Table 2**).⁹ A second study demonstrated that there was not a statistically significant difference in the incidence of stable response between fostamatinib and placebo. There is insufficient evidence on long-term use, bleeding, and transfusion rates and evidence comes from small, manufactured funded studies.
- Patients taking fostamatinib should be monitored for blood pressure increases and monthly liver function tests (LFTs).

Lusutrombopag

- No published trials were available for analysis. Prescribing materials describe two, phase 3, randomized controlled trials in patients with thrombocytopenia and chronic liver disease. One trial included centers in Japan only and the second trial enrolled patients from centers in Japan, Europe and the United States. In the first study (n=97), the primary endpoint was proportion of patients not requiring a platelet transfusion, which was lower with lusutrombopag compared to placebo, absolute risk reduction [ARR] 64% and number needed to treat [NNT] 2.¹⁰ In the second study (n= 215), the number of patients that required no platelet transfusion prior to primary invasive procedure or rescue therapy for bleeding from randomization through 7 days after invasive procedure was 65% for lusutrombopag treated patients and 13% for placebo, ARR 52% and NNT of 2.¹⁰
- The most common adverse event with lusutrombopag was headache and which occurred in 3% or more of patients.¹⁰

Recommendations:

- Clinical evidence for efficacy and harms does not clearly demonstrate superiority of one treatment for thrombocytopenia over another for their corresponding approved indications. Continued monitoring for appropriate utilization is recommended.
- Recommend prior authorization criteria for non-preferred drugs (**Appendix 4**).
- Evaluate costs in executive session to determine PDL status.

Background:

The incidence and prevalence of thrombocytopenia is not clearly defined; however, it is estimated that the incidence of chronic ITP is 100 cases per one million persons per year.⁴ The severity of thrombocytopenia is variable dependent upon the cause, response to therapy, age of onset and potential for spontaneous remission. Thrombocytopenia is caused by a chronic bone marrow failure (myelodysplastic syndromes, primary myelofibrosis, acquired aplastic anemia and inherited bone marrow failure disorders), chemotherapy-induced thrombocytopenia, or immune thrombocytopenia. All types of thrombocytopenia result from a decreased number of platelets and if left untreated can lead to bleeding, bruising and rarely death due to hemorrhage. The goal of therapy in patients with thrombocytopenia is to increase platelet counts to prevent clinically relevant bleeding.

Standard of care for thrombocytopenia is treatment of acute needs with ‘rescue therapies’ (e.g., corticosteroids, intravenous immunoglobulins and platelet infusions) and if needed with ‘active therapies’ (e.g., rituximab, immunosuppressive agents and cytotoxic therapies).² Active treatments are often used as needed to maintain platelet counts, usually checked weekly until stable counts are maintained and then checked on a monthly basis.² Oral glucocorticoid based therapy is recommended first line for short term use; however, chronic glucocorticoid therapy is not recommended due to adverse events.¹ Second-line treatments include: splenectomy, rituximab, TPOs or fostamatinib. Long-term remission may be possible with splenectomy and rituximab but less likely with TPOs. TPOs are generally reserved for chronic use in patients who fail to respond adequately to first-line treatments or choose not to use those therapies. TPOs are also used prior to surgery in patients who need a temporary increase in platelet and don’t respond to glucocorticoids. Benefits and risk of therapy need to be considered with each treatment. Although rare, rituximab has been associated with progressive multifocal leukoencephalopathy.¹ Eltrombopag has a boxed warning for a potential to cause severe and potentially life-threatening hepatotoxicity. Alanine aminotransferase (ALT) elevations and hepatic function should be monitored.¹

The most important outcomes in patients with thrombocytopenia are: platelet counts, bleeding episodes, severe or life-threatening bleeds, mortality, platelet transfusions, and thromboembolisms. A complete response is defined by the International Working Group (IWG) as a platelet threshold of $\geq 100 \times 10^9/L$ and a response is considered ≥ 30 but $< 100 \times 10^9/L$ and a doubling from baseline.¹

Utilization for treatments for thrombocytopenia are low with no claims in quarter 2 and only one claim for eltrombopag in quarter 3. There are no prior authorization criteria for this class.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Thrombopoietin Receptor Agonists			
Avatrombopag (Doptelet®)¹¹ AkaRx, Inc.	- Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.	Platelet count ($\times 10^9/L$): < 40: 60 mg orally 40 to < 50: 40 mg orally	Platelet count ($\times 10^9/L$): <40: 60 mg (3 tablets) daily for 5 days 40 to < 50: 40 mg (2 tablets) daily for 5 days
Eltrombopag (Promacta®)¹² Novartis Pharmaceuticals	- Thrombocytopenia in adults and children (1 year and older) with chronic ITP who have insufficient response to prior therapies* - Thrombocytopenia in patients with chronic hepatitis C to allow initiation and maintenance of interferon-based therapy	<u>For first-line severe aplastic anemia†:</u> Pediatrics 2-5 years old: 2.5 mg/kg orally Pediatrics 6-11 years old: 75 mg orally Patients 12 years and older: 150 mg orally	Adults: Once daily Pediatrics: Once daily

	<ul style="list-style-type: none"> - Patients with severe aplastic anemia who have not responded to immunosuppressive therapy - In combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients (2 years and older) with severe aplastic anemia 	<p><u>For all other indications:</u></p> <p>Adults and pediatrics 6 and older: 25-50 mg orally†</p> <p>Pediatrics (ages 1-5): 25 mg orally†</p>	
Lusutrombopag (Mulpleta®)¹⁰ Shionogi and Co., Ltd.	<ul style="list-style-type: none"> - Thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure 	3 mg orally with or without food	Give once-daily for 7 days, starting 8-14 days before a procedure and the procedure should take place within 2-8 days after the last dose
Romiplostim (Nplate®)¹³ Amgen Inc.	<ul style="list-style-type: none"> - Thrombocytopenia in patients with chronic ITP who have had an insufficient response to prior therapies* - Thrombocytopenia in pediatric patients 1 year of age and older with ITP for at least 6 months who have insufficient response to corticosteroids, immunoglobulins, or splenectomy. 	Adults and Pediatrics: Initial dose is 1 mcg/kg subcutaneously	Once weekly
<i>Tyrosine Kinase Inhibitor</i>			
Fostamatinib (Tavalisse™)¹⁴ Rigel Pharmaceuticals	<ul style="list-style-type: none"> - Thrombocytopenia in adult patients with chronic ITP who had an insufficient response to previous therapy 	100 mg orally – increase after 4 weeks if needed	Twice daily

Key: * corticosteroids, immunoglobulins, or splenectomy; † Adjust based on target platelet count and dose may need to be adjusted based on hepatic impairment and patients of Asian ancestry, ‡ In combination with standard immunosuppressive therapy

Abbreviations: ITP – immune thrombocytopenia

Table 2. Summary of Pivotal Studies Completed.

Study	Comparison	Population	Primary Outcome	Results
Afdhal, et al¹⁵ MC, DB, PC, RCT, Phase 3	Eltrombopag 75 mg daily vs. Placebo daily	Adult patients with thrombocytopenia and chronic liver disease who are undergoing an elective invasive procedure	Avoidance of platelet transfusion before, during and up to 7 days after the procedure	Eltrombopag: 104 (72%) Placebo: 28 (19%) P<0.001 CI not provided ARR 53%

	30 days	(n=292)		NNT 2
Bussel, et al⁹ FIT1	Fostamatinib 100mg twice daily	Adults with persistent and chronic immune thrombocytopenia	Stable Response (platelets \geq 50,000/ μ L in 4 or more of the 6 biweekly visits)	Fostamatinib: 9 (18%) Placebo: 0 (0%) P=0.026 CI not provided ARR 18% NNT 6
MC, PC, DB, RCT, Phase 3	vs. Placebo	(n=101)		
Bussel, et al⁹ FIT2	Fostamatinib 100mg twice daily	Adults with persistent and chronic immune thrombocytopenia	Stable Response (platelets \geq 50,000/ μ L in 4 or more of the 6 biweekly visits)	Fostamatinib: 9 (18%) Placebo: 1 (4%) P=0.152 CI not provided
MC, PC, DB, RCT, Phase 3	vs. Placebo	(n= 74)		
Tarantino, et al¹⁶	Romiplostim weekly*	Children with chronic ITP	Durable platelet response [†]	Romiplostim: 22 (52%) Placebo: 2 (10%) P=0.002 OR 9.1 (95% CI, 1.9 to 43.2) ARR 42% NNT 3
MC, DB, RCT, Phase 3	vs. Placebo weekly	(n=62)		
	24 weeks			
Terrault, et al⁸ ADAPT 1	Avatrombopag 60 mg X 5 days	Adults with thrombocytopenia and chronic liver disease undergoing scheduled procedures	Proportion of patients not requiring platelet transfusion or rescue procedures for bleeding up to 7 days after a scheduled procedure	Avatrombopag 60 mg: 59 (65.6%) Vs. Placebo 60 mg: 11 (22.9%) P<0.001 ARR 43% NNT 3
RCT, DB, PC, MC, Phase 3	vs. Placebo 60 mg	(n=231)		
	Avatrombopag 40 mg X 5 days			Avatrombopag 40 mg: 52 (88.1%) Vs. Placebo 40mg: 13 (38.2%) P<0.001 CI not provided ARR 50 NNT 2
	vs. Placebo 40 mg			
Terrault, et al⁸ ADAPT 2	Avatrombopag 60 mg X 5 days	Adults with thrombocytopenia and chronic liver disease undergoing scheduled procedures	Proportion of patients not requiring platelet transfusion or rescue procedures for bleeding (transfusions, vitamin K, cryoprecipitate, desmopressin,	Avatrombopag 60 mg: 48 (68.6%) Vs. Placebo 60 mg: 15 (34.9%) P<0.001 ARR 34%
RCT, DB, PC, MC, Phase 3	vs. Placebo 60 mg	(n=204)		

	Avatrombopag 40 mg X 5 days vs. Placebo 40 mg		recombinant activated factor VII, amino-caproic acid, tranexamic acid, surgical intervention, or interventional radiology) up to 7 days after a scheduled procedure	NNT 3 Avatrombopag 40 mg: 51 (87.9%) Vs. Placebo: 11 (33.3%) P<0.001 CI not provided ARR 55% NNT 2
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Key: * Dosed weekly from 1 µg/kg to 10 µg/kg to target platelet counts of 50-200x10⁹, † Platelet counts ≥ 50 x 10⁹/L without rescue drug use in the preceding 4 weeks

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; DB – double-blind; ITP – immune thrombocytopenia; MC – multi-center; NNT – number need to treat; OR – odds ratio; PC – placebo-controlled; RCT – randomized controlled trial

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane – Alternative Agents to Prophylactic Platelet Transfusion for Preventing Bleeding in People with Thrombocytopenia Due to Chronic Bone Marrow Failure

A 2016 review by Cochrane analyzed evidence for the use of alternatives to platelet transfusion.⁶ A number of alternatives were included in the search; however, this review will focus on the TPO mimetics, which included 5 trials (n=456). Four romiplostim and one eltrombopag trial were identified. The TPO trials were considered to have a high risk of bias due to funding and conflicts of interest with industry. Patients enrolled had the following diagnosis: MDS; MDS and acute myeloid leukemia (AML) or aplastic anemia; MDS or aplastic anemia and familial thrombocytopenia. There was moderate quality of evidence that the use of TPO mimetics, compared to placebo, resulted in a significant reduction in the number of patients receiving any type of platelet infusion (RR 0.74; 95% CI, 0.61 to 0.95).⁶ The anticipated absolute effects in risk of transfusion was 658 patients per 1000 patients for placebo and 500 patients per 1000 patient for TPOs.⁶ Difference in drug reactions between TPOs and placebo were found to be similar based on low quality evidence (RR 1.12; 95% CI, 0.83 to 1.51).⁶ There was insufficient or very-low quality evidence for the following outcomes: at least one bleeding episode, life-threatening bleed, all-cause mortality, transfusion reactions, and thromboembolic events. Limitations to the evidence include high risk of bias and lack of high quality evidence. Overall, there is insufficient evidence to suggest a benefit TPOs in reducing bleeds in patients with thrombocytopenia due to chronic bone marrow failure.

Cochrane – TPO Receptor Agonists for Chronic Idiopathic Thrombocytopenia Purpura

Cochrane reviewed the evidence for the use of TPOs in chronic ITP in 2011.⁴ Evidence from six studies for the drugs romiplostim and eltrombopag were included. Comparisons were made between TPOs and placebo or standard of care (SOC) (e.g., glucocorticoids, anti-D immune globulin, intravenous immune globulin, rituximab, azathioprine, etc.). Adult and children, median age of early to mid-50s, with a diagnosis of chronic ITP (platelet count less than 30×10^9) were included. Studies were small with a range of 21 to 234 patients in each study and a duration of 6 to 52 weeks.⁴ Overall risk of bias was rated as low for all domains except for “other bias” which included funding by the manufacturer. The primary outcome was overall survival and severe bleeding. Secondary outcomes were; overall platelet response (durable plus transient rates of platelet response), complete response (increase in platelet counts to $> 150 \times 10^9/l$), partial response (increase in platelet count to between 50 and $150 \times 10^9/l$ and durable platelet response (platelet count $\geq 50 \times 10^9/l$).

There was insufficient evidence for the outcome of mortality. Improved overall platelet response was higher in patients treated with TPOs versus comparators, 71% vs 17% (NNT 2), with a RR of 4.06 (95% CI, 2.93 to 5.63) compared to placebo.⁴ When compared to SOC, 92% of patients treated with TPOs had an overall platelet response compared to 51% for SOC (RR of 1.81; 95% CI, 1.37 to 2.37/NNT 3).⁴ A complete response favored TPOs versus placebo (RR 9.29; 95% CI, 2.32 to 37.15) and durable response favored TPOs over placebo as well (RR 14.16; 95%, 2.91 to 69.01); however, these results are associated with wide confidence intervals which suggests the benefit is highly variable. Overall bleeding events were reduced with TPOs compared to placebo 54% vs. 70% (RR of 0.78; 95% CI, 0.68 to 0.89/NNT 7) but were similar when compared to SOC (RR 0.97; 95% CI 0.75 to 1.26).⁴ No differences were found between TPOs and comparisons in significant bleeding events or total adverse events. Limitations to these findings are a small number of studies and number of patients who experienced outcomes. Overall evidence was rated as moderate with no evidence that TPOs reduced significant bleeding events compared to SOC, and there was insufficient evidence for a mortality benefit.

Cochrane – Thrombocytopenia Mimetics for Patients with Myelodysplastic Syndromes

The evidence for TPOs for the use of MDS was evaluated in a 2017 Cochrane review.⁵ Six, double-blind, randomized, placebo controlled trials were identified, which included 746 patients. Drugs included were romiplostim (4 trials) and eltrombopag (2 trials). Comparators were placebo, plus or minus additional therapy (azacitidine, decitabine or lenalidomide). Trials were small with sample sizes ranging from 29 to 356 patients. A majority of patients had low and intermediate complications related to MDS. All trials were found to be high risk of bias due to small sample sizes, imbalances between baseline characteristics, and premature termination of two studies.

There were no differences in mortality rates between TPOs and placebo, 21% vs. 25% (RR 0.97; 95% CI, 0.73 to 1.27), based on low quality evidence.⁵ There is insufficient evidence demonstrating that TPOs induce an acceleration of transformation to AML based on a RR of 1.02 (95% CI, 0.59 to 1.77). There was moderate quality evidence that TPOs reduce the incidence of all bleeding rates, 70% vs. 71% (RR 0.92; 95% CI, 0.86 to 0.99). This translates into a bleeding incidence of 713 out of 1000 patients treated with placebo will experience a bleed compared to 656 out of 1000 patients in the TPO treated group; however, the difference of 1% is small and a clinically significance difference is unlikely. There was no evidence of differences in transfusion rates, adverse events, or serious adverse events between TPOs and placebo. Limitations to this review are similar to other studies of thrombocytopenia which include small sample sizes, high risk of bias and small number of trials available for analysis.

Cochrane – Thrombopoietin Receptor Agonists for Prevention and Treatment of Chemotherapy-induced Thrombocytopenia in Patients with Solid Tumors

A 2017 review done by Cochrane evaluated the use of TPOs for thrombocytopenia due to chemotherapy use in patients with solid tumors.⁷ Six randomized, placebo-controlled trials were included. Trials were found to have a high risk of overall bias and detection bias but low risk of bias for the other domains.

In prevention of chemotherapy-induced thrombocytopenia, mortality rates were not found to be different between TPOs and placebo based on two trials of eltrombopag (RR 1.35; 95% CI, 0.53 to 3.45) (low quality evidence).⁷ There was insufficient evidence to determine a difference in severe or life-threatening bleeds. Trials of romiplostim were small and evidence was insufficient to draw any conclusions. Overall evidence does not support the use of TPOs for the prevention or treatment of thrombocytopenia due to chemotherapy in patients being treated for solid tumors.

Egebaly, et al – Tolerability and Efficacy of Eltrombopag in Chronic ITP

A 2017 systematic review and meta-analysis evaluated the effect of eltrombopag use in children and adult patients with chronic ITP.¹⁷ Six, small trials lasting from 6-24 weeks were included in the review. The median age of participants ranged from 9 years to 60.5 years with fewer male participants compared to females (13-52%).¹⁷ Eltrombopag doses ranged from 30 mg to 75 mg with dose-ranging schedules used in 3 studies. Overall platelet response was the primary endpoint, defined as platelet counts of at least 50 X 10⁹/L. The authors report no conflict with industry and received no funding for the publication. Studies were graded for risk of bias and quality of studies was moderate to high. Publication bias was not able to be determined due to the small number of included studies.

Overall platelet response was higher in the eltrombopag group compared to placebo, 63% vs. 18% (RR 3.42; 95% CI, 2.51 to 4.65; I² = 22%).¹⁷ The incidence of significant bleeding was 21% in the eltrombopag group compared to 37% in patients treated with placebo (RR 0.56; 95% CI, 0.41 to 0.77).¹⁷ Limitations to the review are that only placebo-controlled comparisons are available, studies were small and of short duration and studies were funded by industry.

After review, 5 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control), or outcome studied (e.g., non-clinical).¹⁸⁻²²

Guidelines:

American Society of Hematology 2011 Evidence-based Practice Guideline for Immune Thrombocytopenia

The American Society of Hematology guideline was updated in 2011 to provide recommendations on the diagnosis and management of ITP.¹ Evidence was reviewed and graded using the GRADE system for recommendations (1A, 1B, 1C, 2A, 2B, or 2C). A value of 1 represents a high degree in confidence in evidence for an outcome and a value of 2 represents a lower degree of confidence. A designation of “A” represents a higher level of evidence (i.e., RCT), with the quality of evidence decreasing with “B” and “C” scores. The guideline panel was comprised of authors with no conflicts of interest and no funding was provided from pharmaceutical companies. Overall this guideline was rated as high quality. Treatment recommendations are presented in **Table 3**.

Table. 3 American Society of Hematology Recommendations

Patient Demographic	Recommendation	Grade
<i>Pediatrics (children or adolescents)</i>		
Initial management of pediatric ITP	- Short-term corticosteroids	1B
	- Single dose of IVIg (0.8-1 g/kg)	
	- Anti-D* therapy is not advised in children with a hemoglobin concentration that is decreased due to bleeding or with evidence of autoimmune hemolysis	1C
	- Single dose of anti-D* can be used as first-line treatment in Rh-positive, nonsplenectomized children requiring treatment	2B

Second-line Treatment of Pediatric ITP	- Rituximab is recommended if there is significant ongoing bleeding despite treatment with IVIg, anti-D*, or conventional doses of corticosteroids	2C
	- Rituximab may be an alternative to splenectomy in chronic ITP or for those who don't respond favorably to splenectomy	2C
	- High dose dexamethasone is recommended for patients who have significant ongoing bleeding despite treatment with IVIg, anti-D* or conventional high doses of corticosteroids	2C
	- High dose dexamethasone may also be considered as an alternative to splenectomy or for those who don't respond favorably to splenectomy	2C
Persistent or Chronic ITP or ITP unresponsive to initial measures	- Splenectomy for significant or persistent bleeding and lack of responsiveness or intolerance of other therapies or who have a need for an improved quality of life	1B
Treatment of ITP in Adults		
First-line Treatment of Adults	- Longer courses of corticosteroids or IVIg	2B
	- IVIg use with corticosteroids when a more rapid increase in platelet count is required	2B
	- Either IVIg or anti-D* may be used as first-line treatment if corticosteroids are contraindicated	2C
	- If IVIg is used, the dose should initially be 1g/kg as a one-time dose. This dose may be repeated if necessary	2B
Treatment of Patients Who are Unresponsive to or Relapse After Initial Corticosteroid Therapy		
	- Splenectomy for patients who have failed corticosteroid therapy	1B
	- TPOs for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy	1B
	- TPOs may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not had splenectomy	2C
	- Rituximab may be considered for patients at risk of bleeding who have failed one of therapy such as corticosteroids, IVIg or splenectomy	2C
	- Patients requiring treatment receive either corticosteroids or IVIg	1C
Patients with Secondary-ITP due to HCV		
	- If treatment for ITP is required, the initial treatment should be IVIg	2C
Patients with Secondary-ITP due to HIV		
	- If treatment for ITP is required, the initial treatment should be corticosteroids, IVIg, or anti-D*	2C
	- Splenectomy in preference to other treatments in symptomatic patients who fail corticosteroids, IVIg, or anti-D*	2C

Key: * Anti-D is recommended only in patients who are Rh-positive, who have a negative direct antiglobulin test (DAT) and who have not undergone splenectomy.

Abbreviations: ITP – immune thrombocytopenia; IVIg – intravenous immunoglobulin; TPO – thrombopoietin receptor agonists

NICE – Eltrombopag for the Treating Chronic Immune (idiopathic) Thrombocytopenia Purpura

In 2010 National Institute for Health and Care Excellence (NICE) reviewed the evidence for the safety and efficacy of eltrombopag use in adult patients and was updated in 2018.³ The RAISE trial served as the source for a majority of the clinical information. Clinical guidance recommends the use of eltrombopag if the following conditions are met:

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- Patient's condition is refractory to standard active treatments and rescue therapies or
- Patient has severe disease and a high risk of bleeding that needs frequent courses of rescue therapy

Clinical recommendations were based on the results of 3 placebo-controlled, randomized trials; however, only one was published with individual results (**Table 4**). Eltrombopag was associated with less bleeding of any type compared to placebo, 27% vs. 57%, respectively; however, clinically significant bleeding did not differ between groups (13% vs. 10%). The most common adverse reactions seen with eltrombopag were headache, diarrhea, and nausea. There was insufficient evidence for long-term outcomes and direct comparisons to other treatments for ITP. Eltrombopag has also been associated with increases in alanine aminotransferase (ALT) and hepatic monitoring is recommended.

Table 4. Results of Eltrombopag Randomized Controlled Trials³

Study	Comparison	Population	Result
RAISE	Eltrombopag vs. Placebo (plus standard of care in both groups)	Adult patients with chronic ITP (platelet count less than 30 X 10 ⁹ per liter)	Response to therapy†: Eltrombopag: 52% Placebo: 17% OR 8.2 (95% CI, 3.59 to 18.73; p<0.001)

Key: *Standard of Care – corticosteroids, non-selective immunosuppressants and rescue medication, † platelet count of 50-400 X 10⁹/L
Abbreviations: CI – confidence interval; ITP – idiopathic thrombocytopenia; OR – odds ratio

NICE – Romiplostim for the Treatment of Chronic Immune (idiopathic) Thrombocytopenic Purpura

Romiplostim was reviewed by NICE for the use in adult patients with ITP.² Two double-blind, placebo-controlled trials in patients who also received standard of care consisting of prednisone, azathioprine and danazol were included. One trial studied patients (n=63) who had undergone splenectomy and the second trial was in patients (n=62) who had not had splenectomies (**Table 5**).² Patients were treated weekly for 24 weeks. Durable platelet response, defined as a platelet count of at least 50 X 10⁹ per liter in at least 6 of 8 weekly assessments, was the primary endpoint in both trials.

Table 5. Results of Romiplostim Randomized Controlled Trials²

Study	Comparison	Population	Result
Splenectomized Patients	Romiplostim vs. Placebo (plus standard of care in both groups)	Adult patients with chronic ITP (platelet count less than 15 X 10 ⁹ per liter)	Durable platelet response: Romiplostim: 16 (38.1%) Placebo: 0 (0%)
Non-splenectomized Patients	Romiplostim vs. Placebo (plus standard of care in both groups)	Adult patients with chronic ITP (platelet count less than 18 X 10 ⁹ per liter)	Durable platelet response: Romiplostim: 25 (61%) Placebo: 1 (4.8%)

Abbreviations: ITP – idiopathic thrombocytopenia

Guidance issued by NICE for the use of romiplostim in adults is the same as for eltrombopag²:

- Patient's condition is refractory to standard active treatments and rescue therapies or
- Patient has severe disease and a high risk of bleeding that needs frequent courses of rescue therapy

Romiplostim use is not recommended in patients with recurrence of thrombocytopenia and bleeding after stopping treatment, increased bone marrow reticulum, thrombosis, and loss of response. Pooled severe bleeding events (life threatening or fatal) occurred more often in patients taking placebo compared to romiplostim, 7% vs. 12%, respectively. Health-related quality of life was not statistically different between groups.

After review, 2 guidelines were excluded due to poor quality.^{23,24}

References:

1. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207. doi:10.1182/blood-2010-08-302984
2. National Institute for Health and Care Excellence. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. Technology Appraisal Guidance. April 27, 2011. Available at: nice.org.uk/guidance/ta221. Accessed October 15, 2018.
3. National Institute for Health and Care Excellence. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic pupura (TA293). October 26, 2018. Available at <https://www.nice.org.uk/guidance/ta293>. Accessed October 17, 2018.
4. Zeng Y, Duan X, Xu J, Ni X. TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. *Cochrane Database of Systematic Reviews*. 2011;(7). doi:10.1002/14651858.CD008235.pub2
5. Dodillet H, Kreuzer K-A, Monsef I, Skoetz N. Thrombopoietin mimetics for patients with myelodysplastic syndromes. *Cochrane Database Syst Rev*. 2017;9:CD009883. doi:10.1002/14651858.CD009883.pub2
6. Desborough M, Hadjinicolaou AV, Chaimani A, et al. Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review. *Cochrane Database Syst Rev*. 2016;10:CD012055. doi:10.1002/14651858.CD012055.pub2
7. Zhang X, Chuai Y, Nie W, Wang A, Dai G. Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours. *Cochrane Database Syst Rev*. 2017;11:CD012035. doi:10.1002/14651858.CD012035.pub2
8. Terrault N, Chen Y-C, Izumi N, et al. Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia. *Gastroenterology*. 2018;155(3):705-718. doi:10.1053/j.gastro.2018.05.025
9. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. *Am J Hematol*. 2018;93(7):921-930. doi:10.1002/ajh.25125

10. Mulpleta Prescribing Information. Shionogi Inc., Florham Park, NJ. 2018.
11. Doptelet Prescribing Information. Durham, NC; 2018.
12. Promacta Prescribing Information. Novartis Pharmaceutical Corporation, East Hanover, NJ. 2018.
13. Nplate Prescribing Information. Amgen Inc., Thousand Oaks, CA. 2018.
14. Tavalisse Prescribing Information. Rigel Pharmaceuticals, Inc. South San Francisco, CA. 2018.
15. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *Journal of Medicine*. 2012;367(8):716-724. doi:10.1056/NEJMoa1110709
16. Tarantino MD, Bussel JB, Blanchette VS, et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388(10039):45-54. doi:10.1016/S0140-6736(16)00279-8
17. Elgebaly AS, Ashal GE, Elfil M, Menshawy A. Tolerability and Efficacy of Eltrombopag in Chronic Immune Thrombocytopenia: Meta-Analysis of Randomized Controlled Trials. [Review]. *Clinical & Applied Thrombosis/Hemostasis*. 2017;23(8):928-937. doi:10.1177/1076029616663849
18. Prica A, Sholzberg M, Buckstein R. Safety and efficacy of thrombopoietin-receptor agonists in myelodysplastic syndromes: a systematic review and meta-analysis of randomized controlled trials. [Review]. *Journal of Haematology*. 2014;167(5):626-638. doi:10.1111/bjh.13088
19. Rodeghiero F, Stasi R, Giagounidis A, et al. Long-term safety and tolerability of romiplostim in patients with primary immune thrombocytopenia: a pooled analysis of 13 clinical trials. *Journal of Haematology*. 2013;91(5):423-436. doi:10.1111/ejh.12181
20. Catala-Lopez F, Corrales I, de la Fuente-Honrubia C, et al. Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: Systematic review and meta-analysis of randomized controlled trials. [Review]. *Medicina Clinica*. 2015;145(12):511-519. doi:10.1016/j.medcli.2015.03.014
21. Thrombopoietin-receptor agonists for children with immune thrombocytopenia: a systematic review. - PubMed - NCBI. <https://www.ncbi.nlm.nih.gov/liboff.ohsu.edu/pubmed/28845713>. Accessed November 17, 2018.
22. Cines DB, Gernsheimer T, Wasser J, et al. Integrated analysis of long-term safety in patients with chronic immune thrombocytopenia (ITP) treated with the thrombopoietin (TPO) receptor agonist romiplostim. *Journal of Hematology*. 2015;102(3):259-270. doi:10.1007/s12185-015-1837-6
23. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia.[Erratum appears in Br J Haematol. 2016 Nov;175(3):546; PMID: 27785811]. *Journal of Haematology*. 2016;172(2):187-207. doi:10.1111/bjh.13853

24. Nieto M, Calvo G, Hudson I, et al. The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. *Haematologica*. 2011;96(9):e33-40. doi:10.3324/haematol.2011.048819

Appendix 1: Specific Drug Information

Table 6. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
<i>Thrombopoietin Receptor Agonist</i>				
Avatrombopag (Doptelet®)	TPO receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells increasing platelets	5-6 hours till maximal absorption	<ul style="list-style-type: none"> - Via CYP450 (CYP 2C9) - Fecal 88% - Urine 6% 	Half-life: 19 hours Cmax: 166 ng/mL AUC: 4198 ng.hr/mL
Lusutrombopag (Mulpleta®)	TPO receptor agonist that interacts with receptors to induce the proliferation and differentiation of mega-karyocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation.	6-8 hours	<ul style="list-style-type: none"> - Via CYP4 enzymes and CYP4A11 - Fecal 83% - Urine 1% 	Half-life: 27 hours Cmax: 111 ng/mL AUC: 2931 ng.hr/mL Vd: 39.5 L
Eltrombopag (Promacta®)	TPO receptor agonist which interacts with receptors and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells	2-6 hours with approximately 52% absorbed after oral administration - Food decreases absorption and should be taken on an empty stomach	<ul style="list-style-type: none"> - Via CYP1A2 and CYP2C8 - Feces 59% - Urine 31% 	Half- life: 26-35 hours Cmax: not reported AUC: not reported Vd: not reported
Romiplostim (Nplate®)	TPO receptor agonist which binds and activates TPO receptor	Not reported	<ul style="list-style-type: none"> - Excretion TPO receptor dependent 	Half-life: 3.5 days Cmax: not reported AUC: not reported Vd: not reported
<i>Tyrosine kinase inhibitors</i>				
Fostamatinib (Tavalise™)	Tyrosine kinase inhibitor which ultimately reduces antibody-mediated destruction of platelets.	Bioavailability is 55%	<ul style="list-style-type: none"> - Alkaline phosphatase to active metabolite R406 in the gut - CYP450 - Feces 80% - Urine 20% 	Half-life: 15 hours Cmax: 550 ng/mL AUC: 7080 ng.hr/mL
Abbreviations: AUC – area under the curve; Cmax – maximum concentration; TPO – thrombopoietin receptor agonist; Vd – volume of distribution				

Use in Specific Populations:

Avatrombopag – May cause fetal harm. Breastfeeding not recommended.

Eltrombopag – Breastfeeding not recommended.

Fostamatinib – May cause fetal harm. Breastfeeding not recommended.

Lusutrombopag – Breastfeeding not recommended.

Romiplostim- May cause fetal harm, benefits and risks for nursing mothers should be taken into account when prescribing romiplostim.

Drug Safety:

Boxed Warnings: Eltrombopag has a boxed warning for use in patients with chronic hepatitis C when used in combination with interferon and ribavirin. Use may increase the risk of hepatic decompensation. Eltrombopag may also increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

Risk Evaluation Mitigation (REMs) Strategy Programs: There are no REMs for this class.

Contraindications: There are no contraindications for this class.

Table 7. Summary of Warnings and Precautions.

Warning/Precaution	Avatrombopag	Eltrombopag	Fostamatinib	Lusutrombopag	Romiplostim
Thrombotic complications in patients with chronic liver disease	X	X		X	X
Hepatotoxicity		X			
Increased risk of death and progression to Myelodysplastic Syndromes to Acute Myeloid Leukemia		X			
Increases in blast cell counts and increased risk of progression to Acute Myelogenous Leukemia in patients with Myelodysplastic Syndromes					X
Hypertension			X		
Hepatotoxicity			X		
Diarrhea			X		
Neutropenia			X		
Embryo-fetal toxicity			X		
Formation of neutralizing antibodies if severe thrombocytopenia develops					X

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2018

Search Strategy:

#	Searches	Results
1	avatrombopag.mp.	4
2	lusutrombopag.mp.	6
3	eltrombopag.mp.	489
4	Romiplostim.mp.	421
5	1 or 2 or 3 or 4	722
6	limit 5 to (english language and humans and yr="2007 -Current")	643
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	50

Appendix 3: Key Inclusion Criteria

Population	Patients with thrombocytopenia
Intervention	Thrombopoietin receptor agonists or tyrosine kinase inhibitors
Comparator	Placebo or other treatments for thrombocytopenia
Outcomes	Mortality, overall bleeding, severe bleeding, transfusions, thrombosis
Timing	Before surgery or as needed for chronic thrombocytopenia
Setting	Outpatient

Thrombocytopenia Treatments

Goal(s):

- The goal of this initiative is to ensure thrombopoietin receptor agonists (TPOs) and tyrosine kinase inhibitors are used for their appropriate indications and for recommended treatment durations.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis funded by OHP?	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class.	No: Go to #5

Approval Criteria

5. Is the request for avatrombopag (Doptelet®) or lusutrombopag (Mulpleta®) in a patient who is scheduled to undergo a procedure?	Yes: Approve for a maximum of 5 days for avatrombopag and for a maximum of 7 days for lusutrombopag.	No: Go to #6
6. Is the request for fostamatinib (Tavalisse™) and the patients has failed, or has contraindications to, corticosteroids, IVIg, rituximab, romiplostim and eltrombopag?	Yes: Approve for up to 12 months.	No: Pass to RPh. Deny; recommend trial of treatment(s) recommended in #6.

*P&T/DUR Review: 1/2019 (KS)
Implementation: TBD*