

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Doptelet® (avatrombopag tablets for oral use – Dova/AkaRx)

TAC APPROVAL DATE: 07/03/2019

OVERVIEW

Doptelet, a thrombopoietin receptor agonist (TPO-RA), is indicated for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.¹ Also, Doptelet is indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure. For chronic ITP initiate at 20 mg once daily (QD) and adjust the dose to maintain a platelet count $\geq 50 \times 10^9/L$. Do not exceed a dose of 40 mg QD. For chronic liver disease in patients undergoing a procedure, begin Doptelet dosing 10 to 13 days before the scheduled procedure. The recommended daily dose of Doptelet is based on the patient's platelet count prior to the scheduled procedure. The dose is 60 mg (three tablets) QD for 5 days in patients with a platelet count $< 40 \times 10^9/L$ and 40 mg (two tablets) QD for 5 days for patients with a platelet count of $40 \times 10^9/L$ to $< 50 \times 10^9/L$. Doptelet should be given with food. Patients should undergo their procedure 5 to 8 days after the last Doptelet dose. The safety and efficacy of Doptelet have not been established in pediatric patients.

Clinical Efficacy

The efficacy of Doptelet in adults with chronic ITP was assessed in a Phase III, double-blind, placebo-controlled trial in patients who had previously received one or more therapies and had an average baseline platelet count $< 30 \times 10^9/L$.^{1,2} The median exposure duration was 26 weeks for Doptelet and 6 weeks for patients given placebo. Doptelet-treated patients had a longer duration of platelet counts $\geq 50 \times 10^9/L$ in the absence of rescue therapy compared with patients who received placebo (12.4 vs 0 weeks, respectively; $P < 0.001$). Also, more patients receiving Doptelet had platelet counts $\geq 50 \times 10^9/L$ ($\geq 50,000/\mu L$) at Day 8 compared with patients who received placebo (66% vs. 0.0%, respectively; $P < 0.0001$).

The efficacy of Doptelet for the treatment of thrombocytopenia in patients with chronic liver disease who were scheduled to undergo a procedure was established in two identically-designed, multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 [n = 231] and ADAPT-2 [n = 204]).^{1,3} Patients were assigned to the low baseline platelet count cohort ($< 40 \times 10^9/L$) or the high baseline platelet count cohort (≥ 40 to $< 50 \times 10^9/L$) based on their baseline platelet count. In the trials the FDA-approved dosing was utilized for patients randomized (2:1) to receive Doptelet or placebo. Patients were scheduled to undergo their procedure (low, moderate, or high-bleeding risk) 5 to 8 days after their last treatment dose. In ADAPT-1, patients in the low- and high-baseline platelet count groups had baseline platelet counts of $31 \times 10^9/L$ and $44 \times 10^9/L$, respectively. In ADAPT-2, patients in the low- and high-baseline platelet count groups had baseline platelet counts of $32 \times 10^9/L$ and $44 \times 10^9/L$, respectively. The major efficacy outcome was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. In ADAPT-1, this endpoint was statistically superior for patients given Doptelet compared with placebo (66% for Doptelet 60 mg vs. 23% with placebo and 88% for Doptelet 40 mg vs. 38% with placebo). Also, in ADAPT-2, the endpoint was statistically superior for

patients given Doptelet compared with placebo (69% for Doptelet 60 mg vs. 35% with placebo and 88% for Doptelet vs. 33% with placebo).

Guidelines

The American Society of Hematology (ASH) has an evidence-based practice guideline for immune thrombocytopenia (2011).³ This summary will focus on recommendations in adults. Refer to the guideline for the management of younger patients or in specialized conditions (e.g., pregnancy, pediatrics). Treatment for adults is suggested for newly-diagnosed patients with a platelet count $< 30 \times 10^9/L$. Therapies should be individualized and consider the bleeding severity, the desired time course for platelet increases, and adverse events. For newly-diagnosed adults with ITP, longer courses of corticosteroids are preferred over shorter-courses of corticosteroids or intravenous immunoglobulin (IVIG) as first-line therapy. When a more rapid increase in platelet count is required, IVIG should be used with corticosteroids. If corticosteroids are contraindicated, either IVIG or anti-D immunoglobulin (in appropriate patients) may be used as first-line treatment. For the treatment of adults who do not respond or relapse following initial corticosteroids therapy, several strategies are employed. Splenectomy is recommended for patients who have failed corticosteroids. For patients at risk of bleeding who relapse following splenectomy or who have a contraindicated to splenectomy and have failed at least one other therapy, TPO-RAs can be given. Also, TPO-RAs 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 undergone splenectomy. Rituximab may be an alternative for patients at risk of bleeding who have failed one line of therapy (e.g., corticosteroids, IVIG, or splenectomy). No further treatment is recommended in asymptomatic patients after splenectomy who have achieved platelet counts $> 30 \times 10^9/L$.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Doptelet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Doptelet as well as the monitoring required for adverse events and long-term efficacy, approval may require Doptelet to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Doptelet is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Chronic Immune Thrombocytopenia.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
 - A)** The patient is ≥ 18 years of age; AND
 - B)** The agent is prescribed by or in consultation with a hematologist; AND
 - C)** The patient meets one of the following criteria (i or ii):
 - i.** The patient has tried at least one other therapy. Note: Examples of therapies are corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta®

- (eltrombopag tablets and oral suspension), Nplate® (romiplostim injection for subcutaneous use), Tavalisse™ (fostamatinib tablets), and rituximab; OR
- ii. The patient has undergone splenectomy.

2. **Thrombocytopenia in Patients with Chronic Liver Disease.** Approve for 5 days if the patient meets the following criteria (A, B and C):
- A) The patient is an adult ≥ 18 years of age; AND
- B) The patient has a current platelet count $< 50 \times 10^9/L$ ($< 50,000/\mu L$); AND
- C) The patient is scheduled to undergo a procedure within 10 to 13 days after starting Doptelet therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Doptelet has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Doptelet® tablets [prescribing information]. Durham, NC: AkaRx/Dova Pharmaceuticals; June 2019.
2. Jurczak W, Chojnowski K, Mayer J, et al. Phase 3 randomized study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. *Br J Haematol.* 2018;183(3):479-490.
3. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. *Gastroenterology.* 2018;155:705-718.
4. 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.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	Not applicable.	05/30/2018
Annual revision	The following changes were made: <ol style="list-style-type: none"> 1. Chronic Immune Thrombocytopenia: Criteria were added based on the new indication for use in adults with chronic immune thrombocytopenia in patients who have had an insufficient response to a previous treatment. 2. Conditions Not Recommended for Approval: The condition of chronic immune thrombocytopenia was removed as it is now an FDA-approved indication. 	07/03/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.