09-J3000-02

Original Effective Date: 08/15/18

Reviewed: 12/11/24

Revised: 01/15/25

Subject: Avatrombopag (Doptelet)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Avatrombopag (Doptelet®) is an oral small molecule thrombopoietin (TPO) receptor agonist that increases platelet production by stimulating differentiation of megakaryocytes from bone marrow progenitor cells. In May 2018, the US Food and Drug Administration (FDA) approved avatrombopag for treatment of thrombocytopenia in adults with chronic liver disease (CLD) who are scheduled to undergo a procedure. Avatrombopag is also FDA approved for the treatment of chronic ITP in adults who have had an insufficient response to a previous treatment.

The clinical safety and efficacy of avatrombopag was evaluated in two identical double-blind, placebo controlled studies in patients with CLD. Patients were assigned to a low baseline platelet count cohort (<40 x10^9L) or high baseline platelet count cohort (>40 to <50 x10^9L) and stratified according to hepatocellular cancer (HCC) status and risk of bleeding. Patients with a Model for End-Stage Liver Disease (MELD) score of 24 or less undergoing procedures with varying risk of bleeding were included: low risk (paracentesis, thoracentesis, gastrointestinal endoscopy); moderate risk (liver biopsy, bronchoscopy, ethanol ablation therapy, chemoembolization); and high risk (vascular catheterization, transjugular intrahepatic portosystemic shunt, dental procedures, renal biopsy, biliary interventions, nephrostomy tube placement, radiofrequency ablation, laparoscopic interventions). Patients scheduled for neurosurgical intervention, thoracotomy, laparotomy, or organ resection were excluded. Patients with a history of thrombosis, hematologic disorders, severe cardiovascular disease, low portal vein flow (<10 cm/sec), and those receiving platelets or blood products containing platelets, alternative TPO agonists, antiplatelet therapy, anticoagulants, non-steroidal anti-inflammatory medications, or erythropoietin stimulating agents within 7 days of screening were also excluded. Patients were randomized 2:1 to receive avatrombopag or placebo for 5 days and were scheduled to undergo a procedure 5 to 8 days after the last dose of treatment. The low baseline platelet group received 60 mg of active treatment or placebo and the high baseline platelet group received 40 mg. The main efficacy

outcome was the proportion of patients (responders) 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 trial 1, there were (66%) of patients who achieved the main efficacy endpoint in the low baseline platelet count cohort as compared to 23% in the placebo group ($p < 0.0001$). In trial 2, there were (69%) of patients who achieved the main efficacy endpoint in the low baseline platelet count cohort as compared to 35% in the placebo group ($p = 0.0006$). In trial 1, there were (88%) of patients who achieved the main efficacy endpoint in the high baseline platelet count cohort as compared to 38% in the placebo group ($p < 0.0001$). In trial 2, there were (88%) of patients who achieved the main efficacy endpoint in the low baseline platelet count cohort as compared to 33% in the placebo group ($p < 0.0001$). In both trials, a higher percentage of patients receiving avatrombopag achieved a target platelet count of > 50 $x10^9$L on the day of the procedure and a greater mean change in platelet count from baseline to the day of the procedure as compared to placebo. The most common adverse reactions in patients receiving avatrombopag included pyrexia, abdominal pain, nausea, and headache.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

I. Initiation of avatrombopag (Doptelet®) **meets the definition of medical necessity** when used to treat thrombocytopenia associated with the following conditions:

   A. Chronic liver disease (CLD) and **ALL** of the following are met:

      1. The member's platelet count is less than 50 $x10^9$L
      2. The member is scheduled to undergo an elective procedure with an associated risk of bleeding that would require a platelet transfusion
      3. The elective procedure is scheduled to occur 10 to 13 days after initiation of therapy with avatrombopag
      4. The member does not have a history of thrombosis or a genetic prothrombotic condition (e.g., Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency)
      5. Avatrombopag (Doptelet) is not used concurrently with another thrombopoietin receptor agonist (e.g., romiplostim [Nplate™], eltrombopag [Alvaiz, Promacta], lusutrombopag [Mulpleta])
      6. The dosage does not exceed the following and will be achieved using the fewest number of tablets per day:

         a. Platelet count less than 40 $x10^9$L: 60 mg once daily for 5 days

b. Platelet count greater than or equal to 40 $x10^9$L to less than 50 $x10^9$L: 40 mg once daily for 5 days

B. Chronic immune (idiopathic) thrombocytopenic purpura (ITP) and **ALL** of the following are met:

1. The member has demonstrated an insufficient response to EITHER of the following:
   a. Adequate trial of corticosteroids (e.g., prednisone 1-2 mg/kg for 2-4 weeks)
   b. Immunoglobulins therapy (e.g., intravenous immune globulin [IVIG])
2. **ONE** of the following:
   a. The member's platelet count is less than 30,000
   b. The member has symptomatic bleeding or increased risk for bleeding and platelet count is less than 50,000
3. The member does not have a history of thrombosis or a genetic prothrombotic condition (e.g., Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency)
4. Avatrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., eltrombopag [Alvaiz, Promacta], romiplostim [Nplate], lusutrombopag [Mulpleta])
5. The dosage does not exceed 40 mg daily and will be achieved using the fewest number of tablets per day.

Approval duration: Chronic liver disease -- 60 days; Chronic ITP – 6 months

II. Continuation of avatrombopag (Doptelet®) meets the definition of medical necessity when used for treatment Chronic ITP and ALL of the following are met:

A. The member has been previously approved by Florida Blue or another healthplan in the past 2 years for the treatment of chronic ITP, OR the member has previously met all indication-specific criteria

B. The member has a beneficial response to therapy evidenced by an improvement in platelet count from baseline - documentation must be submitted

C. Avatrombopag is not used concurrently with chronic immune globulin therapy, rituximab, fostamatinib (Tavalisse) or another thrombopoietin receptor agonist (e.g., eltrombopag [Alvaiz, Promacta], romiplostim [Nplate], or lusutrombopag [Mulpleta])

D. The dose does not exceed 40 mg daily and will be achieved using the fewest number of tablets per day.

Approval duration: Chronic ITP – 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Thrombocytopenia in Chronic Liver Disease scheduled to undergo a procedure: Thrombocytopenia in adult patients with chronic liver disease scheduled to undergo a procedure should begin dosing 10 to 13 days prior to a scheduled procedure. Patients should undergo the procedure within 5 to 8 days after the last dose. Take with food once daily for 5 consecutive days and dose is based on platelet count prior to a scheduled procedure. Obtain platelet count prior to administration and on the day of the scheduled procedure to ensure adequate platelet response.

- Platelet count less than 40 $x10^9$L: 60 mg (3 tablets) daily for 5 days
- Platelet count greater than or equal to 40 $x10^9$L to less than 50 $x10^9$L: 40 mg (2 tablets) daily for 5 days

Thrombocytopenia in chronic immune thrombocytopenia (ITP): Thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment should begin 20 mg once daily and adjust the dose or frequency of dosing to maintain platelet count greater than or equal to 50 x 10^9/L. Assess platelets weekly until a stable platelet count is achieved and then monthly therafter. Obtain platelet counts at least 4 weeks following discontinuation. Dose adjust based on the platelet response (see prescribing information for dose level 1 through 6). Do not exceed 40 mg per day. Discontinue if platelet count does not increase to greater than 50 x 10^9/L after 4 weeks of dosing at the maximum dose. Discontinue if the platelet count is greater than 400 x 10^9/L after 2 weeks of dosing at 20 mg once weekly.

Dose Adjustments

See prescribing information for dose titration instructions for the treatment of ITP and for use with moderate or strong dual inhibitors or inducers of CYP2C9 and CYP3A4.

Drug Availability

- 20 mg tablets

PRECAUTIONS:

Contraindications- None

Precautions/Warnings

- Thrombotic and thromboembolic complications in patients with chronic liver disease or chronic ITP have been associated with thrombopoietin receptor agonists. Consider thrombotic risk when administering to patients with known risk factors for thromboembolism including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). Monitor platelet counts and for thromboembolic events.
- Do not administer to patients with chronic liver disease to normalize platelet counts.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

B18.0 – B18.9	Chronic viral hepatitis
C22.0	Hepatocellular carcinoma
D69.3	Immune thrombocytopenic purpura
K70.0 – K70.9	Alcoholic liver disease
K73.0 – K73.9	Chronic hepatitis, not elsewhere classified
K74.0 – K74.69	Fibrosis and cirrhosis of liver
K75.81	Nonalcoholic steatohepatitis
K76.9	Chronic nonalcoholic liver disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the guideline creation.

DEFINITIONS:

None.

RELATED GUIDELINES:

Eltrombopag (Promacta®), 09-J1000-13
Fostamatinib (Tavalisse), 09-J3000-00
Immune Globulin Therapy, 09-J0000-06
Rituximab (Rituxan®), 09-J0000-59
Romiplostim Injection (Nplate™), 09-J0000-88

OTHER:

None applicable.

REFERENCES:

1. Clinical Pharmacology. [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL. www.Clinicalpharamcology-ip.com Accessed 11/30/24.
2. Doptelet (avatrombopag) [package insert]. Dova Pharmaceuticals, Inc. Durham, NC: July 2024.
3. Micromedex ® Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 11/30/24.

4. 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. Doi: 10.1053/j.gastro.2018.05.025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/11/24.

GUIDELINE UPDATE INFORMATION:

08/15/18	New Medical Coverage Guideline.
09/15/19	Review and revision to guideline including update to the position statement, dosing, coding, and references.
12/15/19	Review and revision to guideline including updating the position statement.
12/15/20	Review and revision to guideline including updating the references.
12/15/21	Review and revision to guideline including updating the references.
12/15/22	Review and revision to guideline; consisting of updating documentation of platelet improvement under continuation criteria and updating references.
12/15/23	Review and revision to guideline including updating the position statement and references.
01/15/25	Review and revision to guideline including updating the position statement for risk of bleeding.