Doptelet (avatrombopag)
Policy Number: C16445-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
05/2019	07/31/2019	07/31/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499 (NOC): Prescription drug, oral, non chemotherapeutic, nos	RxPA	Q3 2019 20190828C16445-A

PRODUCTS AFFECTED:
Doptelet (avatrombopag)

DRUG CLASS:
Thrombopoietic agent -Small molecule thrombopoietin (TPO) receptor agonist

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:
Tablet, oral: 20 mg

FDA-APPROVED USES:
Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. Thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: Chronic liver disease-associated thrombocytopenia

REQUIRED MEDICAL INFORMATION:
A. THROMBOCYTOPENIA IN CHRONIC LIVER DISEASE (TICL):
1. The patient has a diagnosis of chronic liver disease-associated thrombocytopenia
   AND
2. The patient is scheduled to undergo a procedure (excluding patients undergoing neurosurgical interventions, thoracotomy, laparotomy, or organ resection)
   AND
3. The medication is being initiated 10 to 13 days prior to the scheduled procedure
   AND
4. The patient is undergoing the procedure 5 to 8 days after the last dose
   AND

5. There is documentation that a platelet count will be obtained prior to therapy administration and on the day of the procedure
   AND
6. The patient has a baseline platelet count <50 x10^9/L AND
7. The medication is NOT being used to normalize platelet counts
   AND
8. The medication is NOT being used concurrently with another thrombopoietic agent
   AND
9. Documentation of historical trial and failure or labeled contraindication to Mulpleta (lusutrombopag)

B. CHRONIC IMMUNE THROMBOCYTOPENIA (CITP):

1. Prescriber attestation of a diagnosis of Chronic ITP
   AND
2. Platelet count less than 20 x 10^9/L (20,000/mm³) OR less than 30 x 10^9/L with ITP whose degree of thrombocytopenia and clinical condition(s) increase the risk of bleeding (e.g. hypertension, renal insufficiency, concomitant antiplatelet agents or anticoagulant medications, alcoholism, infections, undergoing a medical or dental procedure with blood loss anticipation, recent surgery, head trauma). Documentation required.
   AND
3. Documented failure, intolerance or contraindication to ALL of the following ITP treatments:
   (i) Corticosteroids (i.e. prednisone, methylprednisolone, dexamethasone) AND Intravenous immune globulin (IVIG)
   AND
   (ii) ONE immunesuppressive therapy: (i.e. cyclosporine, mycophenolate moefetil, sirolimus,rituximab) OR patient has had splenectomy
   AND
4. Not prescribed for, or intended for, the following: Concurrent use with, another thrombopoietin receptor agonist [e.g., Nplate (romiplostim)] AND An attempt to normalize platelet count
   AND
5. Documentation of historical trial and failure or labeled contraindication to Promacta (eltrombopag)

DURATION OF APPROVAL:
TICL: Initial authorization: 5 days, Continuation of therapy: N/A
CITP: Initial authorization: 3 months, Continuation of therapy: 6 months

QUANTITY:
TICL: Platelet count 40 to <50 x10^9/L mm^3 – 40 mg (2 tablets) once daily for 5 consecutive days,
TICL: Platelet count <40 x10^9/L – 60 mg (3 tablets) once daily for 5 consecutive days
CITP: 20 mg Once Daily Dose can be adjusted or frequency of dosing to maintain platelet count greater than or equal to 50 x10^9 /L. Do not exceed 40 mg per day

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a hematologist, hepatologist or surgeon

AGE RESTRICTIONS:
18 years of age and older

GENDER:

Male and female

CONTINUATION OF THERAPY:
A. THROMBOCYTOPENIA IN CHRONIC LIVER DISEASE (TICL): N/A

B. CHRONIC IMMUNE THROMBOCYTOPENIA (ITP):
1. Documentation of positive clinical response to therapy as evidenced by increase in platelet count to a level sufficient to avoid clinically important bleeding, OR increase or achievement of platelet count to at least ≥ 50 x 10^9/L

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Doptelet are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. There are no contraindications listed in the manufacturer's labeling. There is a potential for increased thrombotic risk when administering Doptelet 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).

OTHER SPECIAL CONSIDERATIONS:
Doptelet should be initiated 10 to 13 days prior to the scheduled procedure. Patients should undergo procedure 5 to 8 days after the last dose. A platelet count should be obtained prior to therapy administration and on the day of the procedure

BACKGROUND:
Doptelet is a small molecule TPO receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in an increased platelet production. It is administered orally as a tablet and is indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.
Efficacy
The efficacy of Doptelet for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 (NCT01972529) and ADAPT-2 (NCT01976104)). In each study, patients were assigned to the Low Baseline Platelet Count Cohort (40 x10 L) or the High Baseline Platelet Count Cohort (≥40 to 50 x10 L) based on their platelet count at Baseline. Patients were then randomized in a 2:1 ratio to either Doptelet or placebo. Patients were stratified according to hepatocellular cancer (HCC) status and risk of bleeding associated with the elective procedure (low, moderate, or high). Patients undergoing neurosurgical interventions, thoracotomy, laparotomy or organ resection were not eligible for enrollment. Patients in the Low Baseline Platelet Count Cohort received 60 mg Doptelet or matching placebo once daily for 5 days, and patients in the High Baseline Platelet Count Cohort received 40 mg Doptelet or matching placebo once daily for 5 days. Eligible patients were scheduled to undergo their procedure (low, moderate, or high bleeding risk) 5 to 8 days after their last dose of treatment. Patient populations were similar between the pooled Low and High Baseline Platelet Count Cohorts and consisted of 66% male and 35% female; median age 58 years and 61% White, 34% Asian, and 3% Black.
In ADAPT-1, a total of 231 patients were randomized, 149 patients were treated with Doptelet and 82 patients were treated with placebo. In the Low Baseline Platelet Count Cohort, the mean Baseline platelet count for the Doptelet-treated group was 31.1 x10 /L and for placebo-treated

patients was 30.7 x10 /L. In the High Baseline Platelet Count Cohort, the mean Baseline platelet count for the Doptelet-treated patients was 44.3 x10 /L and for placebo-treated patients was 44.9 x10 /L.
In ADAPT-2, a total of 204 patients were randomized, 128 patients were treated with Doptelet and 76 patients were treated with placebo. In the Low Baseline Platelet Count Cohort, the mean Baseline platelet count for the Doptelet-treated group was 32.7 x10 /L and for placebo-treated patients was 32.5 x10 /L. In the High Baseline Platelet Count Cohort, the mean Baseline platelet count for the Doptelet-treated patients was 44.3 x10 /L and for placebo-treated patients was 44.5 x10 /L. Across both baseline platelet count cohorts and the avatrombopag and placebo treatment groups, patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk.
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. Responders were defined as patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure. In both baseline platelet count cohorts, patients in the Doptelet treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant. In patients in the Low Baseline Platelet Count Cohort, the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding was 66% (n=90) for Doptelet 60 mg in ADAPT-1 and 69% (n=70) in ADAPT-2. In patients in the High Baseline Platelet Count Cohort, the proportion of subjects not requiring a platelet-transfusion or any rescue procedure for bleeding was 88% (n=59) for Doptelet 40 mg and 88% (n=58) in ADAPT-2.
Safety
The safety of Doptelet was evaluated in two international, identically designed, randomized, double-blind, placebo-controlled trials, ADAPT-1 and ADAPT-2, in which 430 patients with chronic liver disease and thrombocytopenia received either Doptelet (n=274) or placebo (n=156) daily for 5 days prior to a scheduled procedure, and had 1 post-dose safety assessment. Patients were divided into two groups based on their mean platelet count at baseline:
-Low Baseline Platelet Count Cohort (less than 40 x10 /L) who received Doptelet 60 mg once daily for 5 days
-High Baseline Platelet Count Cohort (40 to less than 50 x10 / L) who received Doptelet 40 mg once daily for 5 days
The majority of patients were males (65%) and median subject age was 58 years (ranging from 19-86 years of age). The racial and ethnic distribution was White (60%), Asian (33%), Black (3%), and Other (3%).
The most common adverse reactions (those occurring in ≥3% of patients) in the Doptelet-treated groups (60 mg or 40 mg) across the pooled data from the two trials include pyrexia, abdominal pain, nausea, headache, fatigue, and peripheral edema.
For the Low Baseline Platelet Count Cohort, the incidence of serious adverse reactions was 7% (11/159) in the 60 mg Doptelet treatment group and 13% (12/91) in the matching placebo treatment group. For the High Baseline Platelet Count Cohort, the incidence of serious adverse reactions was 8% (9/115) in the 40 mg Doptelet treatment group and 3% (2/65) in the matching placebo treatment group. The most common serious adverse reaction reported with Doptelet was hyponatremia. Two Doptelet-treated patients (0.7%) developed hyponatremia as compared to no patients in the

combined placebo group. Adverse reactions resulting in discontinuation of Doptelet were anemia, pyrexia, and myalgia; each was reported in a single (0.4%) patient in the Doptelet (60 mg) treatment group.

The efficacy of DOPTELET in adult patients with chronic immune thrombocytopenia was evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT01438840). Patients had previously received one or more prior chronic immune thrombocytopenia therapies and had an average of screening and baseline platelet counts <30 $x10^9$ /L. Patients were centrally stratified by splenectomy status, baseline platelet count (≤15 $x10^9$ /L or >15 $x10^9$/L to <30 $x10^9$/L), and use of concomitant chronic immune thrombocytopenia medication, and then randomized (2:1) to receive either DOPTELET or placebo for 6 months. Patients received a starting dose of 20 mg once daily, with doses subsequently titrated based on platelet response.

Forty-nine patients were randomized, 32 to DOPTELET and 17 to placebo, with similar mean [SD] baseline platelet counts in the 2 treatment groups (14.1 [8.6] $x10^9$/L and 12.7 [7.8] $x10^9$/L, respectively). The median age was 44 years, 63% were female, and 94% were Caucasian, 4% Asian and 2% Black. The median duration of exposure was 26 weeks for DOPTELET-treated patients and 6 weeks for placebo-treated patients. The major efficacy outcome in this trial was the cumulative number of weeks in which the platelet count was ≥50 $x10^9$/L during the 6-month treatment period in the absence of rescue therapy. DOPTELET-treated patients had a longer duration of platelet counts ≥50 $x10^9$ /L in the absence of rescue therapy than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, p<0.0001)

APPENDIX:

REFERENCES:

1. Doptelet Prescribing Information. AkaRx, Inc., Durham, NC. June 2019.
2. 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.
3. Terrault NA, Hassanein T, Howell CD, et al. Phase II study of avatrombopag in thrombocytopenic patients with cirrhosis undergoing an elective procedure. J Hepatol 2014; 61:1253.