PDL DRUG REVIEW

Proprietary Name: Doptelet®
Common Name: avatrombopag
PDL Category: Hematopoietics

Comparable Products	Preferred Drug List Status
Mulpleta	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Avatrombopag, the active ingredient of Doptelet®, is a thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in an increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production.

Indication: For the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, Doptelet® may cause fetal harm when administered to a pregnant woman. The available data on Doptelet® in pregnant women are not sufficient to inform a drug-associated risk of adverse developmental outcomes. Advise pregnant women of the potential risk to a fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 20mg

Recommended Dosage: Begin Doptelet® dosing 10-13 days prior to the scheduled procedure. The recommended daily dose is based on the patients' platelet count prior to the scheduled procedure. Patients should undergo the procedure 5-8 days after the last dose of Doptelet®. It is recommended to obtain a platelet count prior to starting treatment and on the day of a procedure to ensure an adequate increase in platelet count.

Take PO QD for 5 consecutive days with food. If the platelet count is less than 40 X 10^9/L, then take 3 tablets (60mg) QD. If the platelet count is 40 to less than 50 X 10^9/L, then take 2 tablets (40mg) QD. Doptelet® has been studied only as a single 5-day once daily dosing regimen in clinical trials in patients with chronic liver disease. It should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

Drug Interactions: There are currently no drug interactions listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Doptelet®) minus reported % incidence for placebo for the combined baseline platelet count cohorts (<50 X 10^9/L). Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than*

placebo. The most frequently reported adverse event included pyrexia (1%), abdominal pain (1%), nausea (0%), headache (0%), fatigue (1%), and peripheral edema (1%).

Doptelet® is a TPO receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. In clinical trials, there was 1 treatment-emergent event of portal vein thrombosis in a patient (N=1/430) with chronic liver disease and thrombocytopenia treated with Doptelet®. It is recommended to consider the potential increased thrombotic risk when giving Doptelet® to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions. Doptelet® should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: AkaRx, Inc

Analysis: The safety and efficacy of Doptelet® for the treatment of thrombocytopenia were assessed in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 and ADAPT-2) that included patients with chronic liver disease who were scheduled to undergo a procedure. In each study, patients were assigned to the Low Baseline Platelet Count Cohort (<40 X 10^9) or the High Baseline Platelet Count Cohort (≥40 to <50 X 10^9/L) based on the patient's platelet count at baseline. Patients undergoing neurosurgical interventions, thoracotomy, laparotomy, or organ resection were not eligible for enrollment. Those in the Low Baseline Platelet Count Cohort (LBPCC) received 60mg Doptelet® or matching placebo for 5 days while those in the High Baseline Platelet Count Cohort (HBPCC) received 40mg Doptelet® or matching placebo. Patient populations were similar between the pooled Low and High Baseline Platelet Count Cohorts and consisted of 66% male, with the median age 58 years and 61% white.

In study 1 (N=231), the mean baseline platelet count for the Doptelet® group was 31.1 X 10^9/L and it was 30.7 X 10^9/L with the placebo group in the Low Baseline Platelet Count Cohort. In the High Baseline Platelet Count Cohort, the mean baseline platelet count for the Doptelet® group was 44.3 X 10^9/L and it was 44.9 X 10^9/L with the placebo group. In study 2 (N=204), the mean baseline platelet count for the Doptelet® group was 32.7 X 10^9/L and it was 32.5 X 10^9/L with the placebo group in the Low Baseline Platelet Count Cohort. In the High Baseline Platelet Count Cohort, the mean baseline platelet count for the Doptelet® group was 44.3 X 10^9/L and it was 44.5 X 10^9/L with the placebo group. Across both treatment groups and both baseline platelet count cohorts, patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk.

The main 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® groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant. Results can be seen in the table below, which was adapted from the prescribing information.

Low Baseline Platelet Count Cohort (<40 X 10^9/L)				
	ADAPT-1		ADAPT-2	
Endpoint	Doptelet® 60mg (N=90)	Placebo (N=48)	Doptelet® 60mg (N=70)	Placebo (N=43)
Responders	66%	23%	69%	35%
Difference of Proportion vs placebo	43%		34%	
p-value	<0.0001		0.0006	

High Baseline Platelet Count Cohort (≥40 to <50 X 10^9/L)				
	ADAPT-1		ADAPT-2	
Endpoint	Doptelet® 40mg (N=59)	Placebo (N=34)	Doptelet® 40mg (N=58)	Placebo (N=33)
Responders	88%	38%	88%	33%
Difference of Proportion vs placebo	50%		55%	
p-value	<0.0001		<0.0001	

In addition, both studies demonstrated a higher proportion of patients who achieved the target platelet count of ≥50 X 10^9/L on the day of the procedure in both Doptelet®-treated groups vs the placebo groups for both cohorts (Low Baseline Platelet Count Cohort Study 1: 69% vs 4%, respectively, p<0.0001; Study 2: 67% vs 7%, respectively, p<0.0001; High Baseline Platelet Count Cohort Study 1: 88% vs 21%, respectively, p<0.0001; Study 2: 93% vs 39%, p<0.0001).

Both studies demonstrated a greater mean change in platelet counts from baseline to the day of the procedure in both Doptelet®-treated groups vs the placebo groups for both cohorts (Low Baseline Platelet Count Cohort- Study 1: 32 X 10^9/L vs 0.8 X 10^9/L, respectively, p<0.0001; Study 2: 31.3 X 10^9/L vs 3 X 10^9/L, respectively, p<0.0001; High Baseline Platelet Count Cohort- Study 1: 37.1 X 10^9/L vs 1 X 10^9/L, respectively, p<0.0001; Study 2: 44.9 X 10^9/L vs 5.9 X 10^9/L, respectively, p<0.0001).

Place in Therapy: Doptelet® is an oral thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to under a procedure. In clinical trials, there was a significantly greater number in the Doptelet® group as compared with placebo who met the primary endpoint of the proportion not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days after an elective procedure by baseline platelet count.

Doptelet® is one of two new TPO receptor agonists indicated for treatment of thrombocytopenia in patients with chronic liver disease prior to a procedure. Its safety and efficacy appear to be similar to the other new product (lusutrombopag; Mulpleta®) with the most significant differences being the duration of therapy and timing of initiation of therapy prior to the procedure. It is therefore recommended that Doptelet® remain non-preferred (like Mulpleta®) and require prior authorization to confirm appropriate diagnosis and circumstances for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Doptelet [package insert]. Durham, NC: AkaRx, Inc; 2018.