PDL DRUG REVIEW

Proprietary Name: Mulpleta®
Common Name: lusutrombopag
PDL Category: Hematopoietics Chronic ITP

Summary

Pharmacology/Usage: Lusutrombopag, the active ingredient of Mulpleta®, is a thrombopoietin (TPO) receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation.

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 there are no available data on use in pregnant women to inform a drug-associated risk. Use in animal studies resulted in 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: 3mg

Recommended Dosage: Begin Mulpleta® dosing 8-14 days prior to a scheduled procedure. Patients should undergo the procedure 2-8 days after the last dose. It is recommended to obtain a platelet count prior to starting treatment and not more than 2 days before the procedure.

Take 3mg PO QD with or without food for 7 days. Mulpleta® has been studied only as a single 7-day once daily 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 (Mulpleta®) minus reported % incidence for placebo. 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 headache (1%). The incidence of serious adverse events was less with Mulpleta® (5%) than with placebo (7%).

Mulpleta® 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. Portal vein thrombosis was reported in 1% of those treated with Mulpleta® and 1% treated with placebo in 3 randomized trials. The thromboses were not associated with a marked increase in platelet count. Consider the potential increased thrombotic risk when giving Mulpleta® to patients with known risk factors for thromboembolism. In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, Mulpleta® should only be used if the potential benefit to the patient

justifies the potential risk. Mulpleta® should not be administered to patients with chronic liver disease to normalize platelet counts.

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

Manufacturer: Shionogi

Analysis: The safety and efficacy of Mulpleta® for the treatment of thrombocytopenia were assessed in 2 randomized, double-blind, placebo-controlled studies that included adults with chronic liver disease who were scheduled to undergo a procedure. Patients with a platelet count less than 50 X 10^9/L were eligible. Patients were randomized to Mulpleta® 3mg or placebo for up to 7 days and included adults with median age of 60 years.

In study 1, 57% of patients underwent procedures other than liver ablation/coagulation and 43% underwent liver ablation/coagulation. The primary outcome in this study was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure. In study 2, 98% of patients underwent procedures other than liver ablation/coagulation and 2% underwent liver ablation/coagulation. In this study, the primary outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding (i.e. platelet preparations, other blood preparations, including red blood cell and plasma, volume expanders) from randomization through 7 days after the primary invasive procedure. In both trials, responders were defined as patients who had a platelet count of ≥50 X 10^9/L with an increase of ≥20 X 10^9/L from baseline. Results can be seen in the tables below, which was adapted from the prescribing information.

Endpoint	Trial 1		Treatment Difference; p-value
	Mulpleta® 3mg (N=49)	Placebo (N=48)	
Not requiring platelet transfusion prior to invasive procedure	78% (N=38/49)	13% (N=6/48)	64%; p<0.0001
Responder during study	76% (N=37/49)	6% (N=3/48)	68%; p<0.0001

Endpoint	Trial 2		Treatment Difference; p-value
	Mulpleta® 3mg (N=108)	Placebo (N=107)	
Not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding from randomization through 7 days after procedure	65% (N=70/108)	29% (N=31/107)	37%; p<0.0001
Responder during study	65% (N=70/108)	13% (N=14/107)	52%; p<0.0001

The median duration of platelet count increase to at least 50 X 10^9/L was 22 days in Mulpleta®-treated patients without platelet transfusion and 1.8 days in placebo-treated with patients with platelet transfusion in study 1 and 19 days in Mulpleta®-treated patients without platelet transfusion and 0 days in placebo-treated patients with platelet transfusion in study 2.

Place in Therapy: Mulpleta® is an oral thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. In clinical trials, there was a significantly greater number who met the primary endpoints and a significantly larger number of responders with Mulpleta® as compared with placebo, with responders defined as patients who had a platelet count of ≥50 X 10^9/L with an increase of ≥20 X 10^9/L from baseline.

Mulpleta® 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

(avatrombopag; Doptelet®) with the most significant differences being the duration of therapy and timing of initiation of therapy prior to the procedure. It is recommended that Mulpleta® remain non-preferred to ensure it is used in clinically appropriate situations.

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

References

[1] Mulpleta [package insert]. Florham Park, NJ: Shionogi Inc; 2018.