Drug Monograph

Drug/Drug Class:	**Mulpleta® (lusutrombopag) tablet / Thrombopoietin Receptor Agonist**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Mulpleta® is available as a 3 mg film coated oral tablet. Distributed by: Shionogi Inc., Florham Park, New Jersey 07932.
Summary of Findings:	The safety and efficacy of Mulpleta® was assessed in two randomized, double-blind, placebo-controlled trials in patients with chronic liver disease who were scheduled to undergo a procedure. In one study, 78% of patients receiving Mulpleta® required no platelet transfusion prior to an invasive procedure, compared with 13% who received placebo and seventy-six percent of Mulpleta®-treated patients were considered responders (platelet count of ≥50 x 10^9/L with an increase of ≥20 x 10^9/L from baseline) vs 6% of patients in the placebo arm. In another study, 65% of patients who received Mulpleta® required no platelet transfusion prior to an invasive procedure or rescue therapy for bleeding through 7 days after the procedure, compared with 29% receiving placebo. Sixty-five percent of Mulpleta®-treated patients were considered responders vs 13% of patients in the placebo group. The most common adverse events in clinical trials was headache.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Preferred Agent ☐ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Thrombocytopenia (platelet count <150,000/microL) is a common complication in patients with chronic liver disease that has been observed in up to 76% of patients. Moderate thrombocytopenia (platelet count, 50,000/microL-75,000/microL) occurs in approximately 13% of patients with cirrhosis. Multiple factors can contribute to the development of thrombocytopenia, including splenic platelet sequestration, bone marrow suppression by chronic hepatitis C infection, and antiviral treatment with interferon-based therapy. Reductions in the level or activity of the hematopoietic growth factor thrombopoietin may also play a role. Thrombocytopenia can impact routine care of patients with chronic liver disease, potentially postponing or interfering with diagnostic and therapeutic procedures including liver biopsy, antiviral therapy, and medically indicated or elective surgery.

Dosage Form [1,3]

Mulpleta® is available as a 3 mg film coated oral tablet.

Manufacturer [1]

Distributed by: Shionogi Inc., Florham Park, New Jersey 07932.

Indication(s) [1]

Mulpleta® is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

Clinical Efficacy [1,3] (mechanism of action/pharmacology, comparative efficacy)

Mulpleta® is an orally bioavailable, small molecule thrombopoietin receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased platelet production.

Pharmacokinetics:

	Mulpleta®
Protein Binding	>99.9%
Volume of Distribution	39.5 L
Metabolism	Hepatic, Primarily CYP4 enzymes, including CYP4A11
Excretion	Urine, ~1% Feces, 83% (16% Unchanged drug)
Half-life	~27 hours

Clinical Trials:

L-PLUS 1

STUDY DESIGN	Randomized, double-blind, placebo-controlled trial (N=97).
INCLUSION CRITERIA	Adult patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50 x 10^9/L.
EXCLUSION CRITERIA	Patients undergoing laparotomy, thoracotomy, open-heart surgery, craniotomy, or organ resection. Patients with a history of splenectomy, partial splenic embolization, or thrombosis and those with Child-Pugh class C liver disease, absence of hepatopetal blood flow, or a prothrombotic condition other than chronic liver disease.
TREATMENT REGIMEN	Patients were randomized 1:1 to receive 3 mg of Mulpleta® or placebo once daily for up to 7 days. The major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure. 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	78% of patients (38/49) receiving Mulpleta® required no platelet transfusion prior to the invasive procedure, compared with 13% (6/48) who received placebo (treatment difference: 64%; P <.0001). Seventy-six percent of Mulpleta®-treated patients were considered responders vs 6% of patients in the placebo arm (treatment difference: 68%; P <.0001).
SAFETY	The most common adverse reaction associated with therapy was headache.

L-PLUS 2

STUDY DESIGN	Randomized, double-blind, placebo-controlled trial (N=215).
INCLUSION CRITERIA	Adult patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50 x 10^9/L.
EXCLUSION CRITERIA	Patients undergoing laparotomy, thoracotomy, open-heart surgery, craniotomy, or organ resection. Patients with a history of splenectomy, partial splenic embolization, or thrombosis and those with Child-Pugh class C liver disease, absence of hepatopetal blood flow, or a prothrombotic condition other than chronic liver disease.

TREATMENT REGIMEN	Patients were randomized 1:1 to receive 3 mg of Mulpleta® or placebo once daily for up to 7 days. The major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. 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	65% (70/108) of patients who received Mulpleta® required no platelet transfusion prior to the invasive procedure or rescue therapy for bleeding through 7 days after the procedure, compared with 29% (31/107) receiving placebo (treatment difference: 37%; P <.0001). Sixty-five percent of Mulpleta®-treated patients were considered responders vs 13% of patients in the placebo group (treatment difference: 52%; P <.0001).
SAFETY	The most common adverse reaction associated with therapy was headache.

Contraindications (1)

- There are no contraindications listed per the manufacturer labeling.

Warnings and Precautions (1,3)

- Thromboembolism: Thrombotic and thromboembolic complications with thrombopoietin receptor agonist use have occurred in patients with chronic liver disease. Thromboses were not associated with a marked increase in platelet count. Due to the potential for increased thrombotic risks, use with caution in patients with known risk factors for thromboembolism (eg, Factor V Leiden, prothrombin 20210A, antithrombin deficiency or protein C or S deficiency). In clinical trials, treatment-emergent portal vein thrombosis was reported (rare). Mulpleta® should only be used if the potential benefit justifies the risk in patients with ongoing or prior thrombosis or absence of hepatopetal blood flow.
- Do not administer to patients with chronic liver disease in an attempt to normalize platelet counts.
- Pregnancy: Although there is no available data in pregnant women, adverse events were observed in animal reproduction studies.
- Breast Feeding: It is not known if Mulpleta® is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for at least 28 days after the last Mulpleta® dose.

Adverse Effects (1)

Most common, ≥ 3%	Mulpleta® 2mg (n=171) %	Placebo (N=170) %

Headache	5	4

The incidence of serious adverse events was 5% (9 of 171 patients) in the Mulpleta® group and 7% (12 of 170 patients) in the placebo group. The most common serious adverse reaction reported with Mulpleta® was portal vein thrombosis. No adverse reactions resulted in discontinuation of Mulpleta®.

Drug Interactions [3]

- There are no significant drug interactions.

Dosage and Administration [1,3]

Begin Mulpleta® dosing 8-14 days prior to a scheduled procedure. Patients should undergo their procedure 2-8 days after the last dose.

The recommended dosage of Mulpleta® is 3 mg taken orally once daily with or without food for 7 days.

In the case of a missed dose, Mulpleta®, should be administered as soon as possible on the same day and return to the normal schedule the following day.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/7-Day Course
lusutrombopag	Mulpleta®	Shionogi	3 mg	$8,500.00

** Wholesale Acquisition Cost

Conclusion

Mulpleta® is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. Two randomized, double-blind, placebo-controlled trials (N=312) demonstrated decreased need for platelet transfusions prior to invasion procedures and increased platelet count in patients receiving Mulpleta®. Furthermore, one of these studies also demonstrated decreased need for rescue therapy for bleeding through day seven post-procedure. The most common adverse event in clinical trials was headache.

Recommendation

The Division is recommending adding Mulpleta to the state specific PDL as a preferred agent.

References

1) Product Information: Mulpleta® (lusutrombopag). Shionogi Inc., Florham Park, New Jersey 07932.
2) Afdhal N, McHutchison J, et al. Thrombocytopenia Associated with Chronic Liver Disease, J Hepatol. June 2008;48(6):1000-7.
3) Lusutrombopag: Drug Information (Lexicomp) Wolters Kluwer Health.

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