Drug Monograph

Drug/Drug Class:	**Opsumit™ (macitentan) Tablets/ endothelin (ET) receptor antagonist**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **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:	Each 10 mg tablet of Opsumit™ contains 10 mg of macitentan. Actelion Pharmaceuticals US, Inc., South San Francisco, CA 94080
Summary of Findings:	Opsumit™ is an orally administered ET receptor antagonist approved for the treatment of pulmonary arterial hypertension (PAH) in adults to delay disease progression, including death, initiation of prostanoid therapy, or clinical worsening. Opsumit™ is the first ET receptor antagonist for PAH that had a primary endpoint of morbidity and mortality, rather than a short-term endpoint of exercise capacity, in the clinical trial.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

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, payors 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

Pulmonary arterial hypertension (PAH) is an increase of blood pressure in the pulmonary arteries leading to shortness of breath, dizziness, fainting, leg swelling and other symptoms. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure.

Dosage Form(s)[1]

Each 10 mg tablet of Opsumit™ contains 10 mg of macitentan.

Manufacturer

Actelion Pharmaceuticals US, Inc., South San Francisco, CA 94080

Indication(s)[1]

Opsumit™ is indicated for the treatment of PAH (WHO Group I) in adults to delay disease progression, including death, initiation of prostanoid therapy, or clinical worsening.

Clinical Efficacy[1,2] (mechanism of action/pharmacology, comparative efficacy)

Opsumit™ is an endothelin (ET) receptor antagonist with a high affinity for and sustained occupancy period of ET receptors in pulmonary arterial smooth muscle cells. Endothelin-1 causes inflammation, hypertrophy, vasoconstriction, fibrosis, and proliferation when it binds to ET-A and ET-B receptors.

	Opsumit™
Protein binding	> 99%
Volume of distribution	50 L, macitentan; 40 L, active metabolite
Metabolism	Liver, via CYP3A4 (major) and CYP2C19 to active metabolite.
Excretion	Urine (50%), inactive metabolites
Half-life	Feces (24%)

The efficacy of Opsumit™ for the treatment of PAH was established in the phase 3, randomized, double-blind, placebo-controlled Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcomes (SERAPHIN) trial. Opsumit™ was effective in slowing the progression of symptomatic PAH compared with placebo.

PULMONARY ARTERIAL HYPERTENSION - SERAPHIN TRIAL

STUDY DESIGN	Randomized, double-blind, placebo-controlled, phase 3 study (n=742).
INCLUSION CRITERIA	Patients 12 years or older with symptomatic PAH.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive placebo (n=250), Opsumit™ 3 mg (n=250), or Opsumit™ 10 mg (n=242) once daily for approximately 2 years. Participants (mean age, 45.6 years; 76.5% female) were primarily in WHO functional class II (52.4%) or III (45.6%), and most were receiving baseline therapy for PAH with a stable dose of oral phosphodiesterase inhibitors (61.4%) or inhaled or oral prostanoids (5.4%). The primary endpoint was the composite of time to the first occurrence of a significant morbidity event (ie, atrial septostomy, lung transplantation, or initiation of IV or subQ prostanoid therapy), worsening of PAH (defined as sustained decrease in 6-minute walk distance (6MWD) of 15% or greater from baseline, plus worsening of PAH symptoms, plus the need for additional PAH treatment), or death from any cause.
RESULTS	The primary endpoint occurred in 31.4% of patients in the Opsumit™ 10 mg group compared with 46.4% of patients in the placebo group (hazard ratio (HR), 0.55; 97.5% CI, 0.32 to 0.76; $p < 0.001$), and in 38% of the Opsumit™ 3 mg group (HR when compared with placebo, 0.7; 95% CI, 0.52 to 0.96; p=0.01). In the Opsumit™ 10 mg, Opsumit™ 3 mg, and placebo groups, worsening of PAH occurred in 24.4%, 28.8%, and 37.2% of patients, respectively, and IV or subQ prostanoid therapy was initiated in 0.4%, 0.4%, and 2.4% of patients, respectively. PAH-related death or hospitalization was also significantly reduced with macitentan 10 mg daily compared with placebo (20.7% versus 33.6%; HR, 0.5; 97.5% CI, 0.34 to 0.75; $p < 0.001$) and with Opsumit™ 3 mg compared with placebo (26% versus 33.6%; HR, 0.67; 97.5% CI, 0.46 to 0.97; p=0.01). At month 6, improvement of WHO functional class from baseline was observed in 22%, 20%, and 13% of patients in the Opsumit™ 10 mg, Opsumit™ 3 mg, and placebo groups, respectively.
SAFETY	The most common side effects that were reported more frequently in the Opsumit™ groups were headache, anemia, upper respiratory infection, nasopharyngitis, and bronchitis.

Contraindications[1]

- Pregnancy; may cause fetal harm

Warnings and Precautions[1]

- Female patients of reproductive potential; may cause fetal harm; exclude pregnancy prior to, monthly during, and 1 month after treatment; prevent pregnancy with highly effective contraception.
- Special restricted distribution program under REMS due to potential for serious birth defects; prescribers, female patients, and pharmacies are required to enroll.

- Anemia, severe; use not recommended.
- Concomitant strong CYP3A4 inhibitors or inducers; avoid use.
- Hemoglobin and hematocrit decreases have been reported; monitoring recommended.
- Hepatotoxicity, liver failure, or elevated aminotransferases may occur; monitoring recommended; discontinuation of therapy may be necessary.
- Pulmonary veno-occlusive disease (PVOD) may occur; discontinue use if confirmed.

Adverse Effects[1]

Most common, >= 3%	Opsumit™ (n=242)	Placebo (n=249)
▪ Nasopharyngitis/pharyngitis	20%	13%
▪ Headache	14%	9%
▪ Anemia	13%	3%
▪ Bronchitis	12%	6%
▪ Urinary tract infection	9%	6%
▪ Influenza	6%	2%

Drug Interactions[1]

- CYP3A4 inducers, strong: rifampin
- CYP3A4 inhibitors, strong: ketoconazole, ritonavir

Dosage and Administration[1]

The recommended dose is 10 mg orally once daily.

Cost

The cost per tablet, regardless of strength, is $228.00 each. WholesaleAcquisitionCost

Conclusion

Opsumit™ is an orally administered ET receptor antagonist approved for the treatment of PAH (WHO Group I) in adults to delay disease progression, including death, initiation of prostanoid therapy, or clinical worsening. Opsumit™ is the first ET receptor antagonist for PAH that had a primary endpoint of morbidity and mortality, rather than a short-term endpoint of exercise capacity, in the clinical trial. Opsumit™ was proven to significantly reduce morbidity and mortality compared with placebo in the phase 3 SERAPHIN trial. It was well-tolerated compared with placebo. Female patients, along with prescribers and pharmacies, must enroll in a REMS program to mitigate the potential for embryofetal toxicity.

Recommendation

The Division recommends this product be considered for inclusion to the state specific PDL edit and it is currently under solicitation.

References

1. Product Information: Opsumit®, macitentan. Actelion Pharmaceuticals US, Inc, South San Francisco, CA, 10/2013.

2. Pulido T, Adzerikho I, Channick RN et al: Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369(9):809-818.

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