PDL NEW DRUG REVIEW

Proprietary Name: Opsumit®
Common Name: macitentan
PDL Category: Pulmonary Anti-Hypertensives

Comparable Products	Preferred Drug List Status
Letairis	Preferred with Conditions
Tracleer	Preferred with Conditions

Summary

Indications and Usage: Treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression. Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Hospitalization for PAH was also reduced with treatment. Effectiveness of macitentan was established in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years and used as either monotherapy or in combination with a PDE5-inhibitor or inhaled prostanoid. This is a pregnancy category X medication. Treatment in women of reproductive potential should only be initiated after a negative pregnancy test. Additionally, a pregnancy test should be performed monthly during treatment. Due to the risk of embryo-fetal toxicity, Opsumit® is only available to females through a restricted program called the Opsumit® REMS Program. Further information on this can be found at www.OPSUMITREMS.com. As other ERAs have caused effects on spermatogenesis, it is also recommended that men be counseled on the potential effects on fertility if Opsumit® is prescribed. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: The concomitant use of strong CYP3A4 inducers, such as rifampin, with macitentan should be avoided. The concomitant use of strong CYP3A4 inhibitors, such as ketoconazole, should also be avoided. It is recommended to use other PAH treatment options if a strong CYP3A4 inhibitor is included as part of an HIV treatment regiment (as many HIV drugs are strong CYP3A4 inhibitors, i.e. protease inhibitors).

Dosage Forms: Tablets, Film-Coated: 10mg

Recommended Dosage: Take one tablet (10mg) once daily; doses greater than 10mg daily have not been studied and are thus not recommended. Treatment in women of reproductive potential should only be initiated after a negative pregnancy test. Additionally, a monthly pregnancy test during treatment should also be performed.

No information was found regarding the need for dose adjustment in those with renal or hepatic impairment; however, elevated liver enzymes were reported in clinical trials (please refer to the adverse events section). It is recommended to discontinue Opsumit® treatment if clinically significant elevations or if elevations are accompanied by an increase in bilirubin >2X upper normal limit (UNL). If hepatic enzyme levels normalize and there are no clinical symptoms of hepatotoxicity, re-starting Opsumit® treatment may be considered.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Opsumit®) minus reported % incidence for placebo.* The most commonly reported adverse events include anemia (10%), nasopharyngitis/pharyngitis (7%), bronchitis (6%), headache (5%), influenza (4%), and urinary tract infection (3%).

Elevated aminotransferases were reported during Opsumit studies: >3X UNL (0%), and >8 times UNL (1.7%). Discontinuations due to hepatic adverse events were reported in studies as well (1.7%). It is thus recommended to obtain lever enzyme tests prior to starting treatment and then periodically as clinically indicated.

Contraindications: Pregnancy, as treatment may cause fetal harm

Manufacturer: Actelion Pharmaceuticals US, Inc.

Analysis: Macitentan, the active ingredient of Opsumit®, is an endothelin receptor antagonist (ERA). As an antagonist, it prevents the binding of endothelin-1 (ET-1) to both endothelin-A (ET_A) and endothelin-B (ET_B) receptors. Macitentan has high affinity to the ET receptors in human pulmonary arterial smooth muscle cells.

Macitentan has a box warning regarding the risk of embryo-fetal toxicity and thus should not be given to a pregnant female due to the risk of fetal harm. It is recommended that females of reproductive potential be given a pregnancy test prior to starting treatment, once monthly during treatment, and 1 month after stopping treatment. Additionally, acceptable methods of contraception should be used to prevent pregnancy during treatment. Last, Opsumit® is only available to females through a restricted program called the Opsumit® Risk Evaluation and Mitigation Strategy (REMS).

One long-term, placebo-controlled study was performed to assess the safety and efficacy of macitentan on the progression of PAH in adults (N=742) with symptomatic PAH (WHO functional class II-IV; II-52%, III-46%, and IV-2%). The primary endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplant, initiation of IV or SC prostanoids), or 'other worsening of PAH'. Other worsening was defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD; worsening of PAH symptoms (worsening of WHO FC); and the need for additional treatment for PAH. Time to PAH death or PAH hospitalization was a secondary outcome.

Results suggested that there was a 45% reduction in the occurrence of the primary endpoint in the macitentan group compared to placebo (hazard ratio [HR] 0.55; p<0.0001). The beneficial effect of macitentan was mostly due to a reduction in clinical worsening events (deterioration in 6MWD and worsening of PAH symptoms and the need for additional PAH treatment). Specifically, 31.4% of the macitentan group had a primary endpoint event as compared with 46.4% of the placebo group; 24.4% vs 37.2%, respectively had worsening PAH; 6.6% vs 6.8%, respectively, ended in death; and 0.4% vs 2.4%, respectively needed IV/SC prostanoid.

The risk of PAH related death or hospitalization for PAH, a secondary endpoint, was reduced by 50% in the macitentan group vs placebo (HR 0.50; p<0.0001). Specifically, 20.7% of the macitentan group ended in death due to hospitalization or hospitalization for PAH vs 33.6% of the placebo group; 2.1% vs 2.0%, respectively, ended in death due to PAH; 18.6% vs 31.6%, respectively, were hospitalized for PAH. Other outcomes assessed included the 6MWD, and macitentan resulted in a placebo-corrected mean increase of 22m at month 6 (p=0.0078). By month 6, 22% of the macitentan group had an improvement of at least one WHO Functional Class as compared with 13% of the placebo group.

There is no evidence at this time to support that Opsumit® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Opsumit® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**
- ☐ **Preferred with Conditions**

References

[1] Opsumit [package insert]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2013.