PDL NEW DRUG REVIEW

Proprietary Name: Sirturo®
Common Name: bedaquiline fumarate
PDL Category: Antimycobacterial

Comparable Products	Preferred Drug List Status
Amikacin	Preferred
Avelox	Non-Preferred
Ethambutol	Preferred
Pyrazinamide	Preferred

Summary

Indications and Usage: To be used as part of a combination therapy in adults with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve its use for when an effective treatment regimen cannot otherwise be provided. It should be administered by directly observed therapy (DOT). The safety and efficacy of Sirturo® for the treatment of latent infection due to *Mycobacterium tuberculosis* and for the treatment of drug-sensitive TB have not been established. Additionally, the safety and efficacy of Sirturo® for the treatment of infections caused by non-tuberculosis mycobacteria (NTM) have not been established. Thus, use in these settings is not recommended. This is a pregnancy category B medication. The safety and efficacy of use in children under 18 years of age have not been established.

Drug Interactions: Bedaquiline is metabolized by CYP3A4. The concomitant use of rifamycins (rifampin, rifapentine, and rifabutin) or other strong CYP3A4 inducers should be avoided. The use of strong CYP3A4 inhibitors (eg ketoconazole) for more than 14 consecutive days should be avoided while on Sirturo®, unless the benefit outweighs the risk. Clinical monitoring is recommended. The use of Sirturo® with Kaletra (lopinavir/ritonavir) should be done with caution and only if the benefit outweighs the risk. Sirturo® prolongs the QT interval; concomitant use with other QT prolonging drugs (ie fluoroquinolones and macrolide antibacterials) can cause additive or synergistic QT prolongation. ECGs should be monitored closely.

Dosage Forms: Tablets: 100mg

Recommended Dosage: Sirturo® should be used in combination with at least 3 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible *in vitro*. If in vitro testing results are not available, treatment may be started with Sirturo® in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible.

The recommended dose is 400mg once daily with food and water weeks 1-2, then 200mg three times per week with food (at least 48 hours between doses) for a total dose of 600mg per week. Treatment duration should be 24 weeks total, and alcohol use should be avoided while on treatment.

Dosage adjustments are not required in those with mild or moderate renal or hepatic impairment; however, Sirturo® should be used with caution in those with severe renal impairment or end stage renal disease (ESRD), and it should be used with caution in those with severe hepatic impairment. It is recommended to monitor Sirturo®-related adverse reactions.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse event reported with Sirturo® included nausea (6.1%), arthralgia (10.7%), headache (15.5%), transaminases increased (7.7%), blood amylase increased (1.3%), hemoptysis (6.6%), chest pain (4%), anorexia (5.2%), and rash (3.9%).

In clinical study 1 (see analysis section for full details), a statistically significant increased mortality risk was seen in the Sirturo® group by week 1 vs placebo (11.4% [N=9/79] vs 2.5% [2/81]; p=0.03). Five deaths from the Sirturo® group and 2 from the placebo group were TB=related. As such, Sirturo® has a boxed warning regarding the risk of increased risk of death with use, and to only use Sirturo® when an effective treatment regimen cannot otherwise be provided.

In clinical study 1, the mean increase in QTc was greater in the Sirturo® group vs placebo from the first week of treatment (9.9ms at week 1 with Sirturo® vs 3.5ms for placebo); the largest increase in QTc during the 24 week study was at week 18 (15.7ms with Sirturo® vs 6.2ms for placebo). Even after treatment was stopped, QT increases from baseline persisted in the Sirturo® group. Sirturo® has a boxed warning regarding the risk of QT prolongation that can occur with use. Additionally, use with drugs that prolong the QT interval may cause additive QT prolongation. An ECG should be obtained prior to starting treatment with Sirturo®, and at least 2, 12, and 24 weeks after starting treatment. Serum potassium, calcium, and magnesium should be measured at baseline and corrected if abnormal.

Contraindications: There are currently no contraindications listed with Sirturo®.

Manufacturer: Janssen

Analysis: Bedaquiline, the active ingredient of Sirturo®, is a diarylquinolines antimycobacterial agent. It inhibits mycobacterial adenosine 5'-triphospate (ATP) synthase, which is an enzyme that is needed for the generation of energy in *Mycobacterium tuberculosis*.

Safety and efficacy of bedaquiline was established in Study 1, a randomized, double-blind, placebo-controlled study that included newly diagnosed patients with multi-drug resistant pulmonary *Mycobacterium tuberculosis* (N=160) and on a combination of 5 other antimycobacterial agents (ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative). At week 24, 77.6% of the Sirturo® group had treatment success (sputum culture conversion) vs 57.6% of the placebo group. This difference was statistically significant (p=0.014). Treatment failure at this same time point was 22.4% vs 42.4%, respectively. At week 72, treatment success was 70.1% in the Sirturo® group vs 56.1% of the placebo group, which was not statistically significantly different (p=0.092). Treatment failure at this same time point was 29.9% vs 43.9%, respectively. Those in the Sirturo® group had a decreased time to culture conversion vs placebo at week 24, with the median time to culture conversion being 83 days with Sirturo® vs 125 days for placebo.

Study 2 was a smaller and shorter duration study comparing Sirturo® with placebo, and both were used in combination with other drugs used to treat MDR-TB (N=47). The Sirturo® group had a decreased time to culture conversion and improved culture conversation rates vs placebo at week 8. The differences in culture conversion at

week 8 between treatments was 38.9% (p=0.004), which was statistically significantly different. The difference at week 24 was 15.7%, which was not statistically significantly different (p=0.32).

It is recommended that Sirturo® remains non-preferred to verify diagnosis and that it's being used as combination therapy.

PDL Placement:

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

References

[1] Sirturo [package insert]. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP; 2013.