

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIRTURO™ safely and effectively. See full prescribing information for SIRTURO.

SIRTURO™ (bedaquiline) Tablets
Initial U.S. Approval – 2012

WARNINGS:

See Full Prescribing Information for complete boxed warning.

- An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.
- QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.

INDICATIONS AND USAGE

SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO is not indicated for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis. (1)

DOSAGE AND ADMINISTRATION

400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks with food. Swallow SIRTURO tablets whole with water. (2)

DOSAGE FORMS AND STRENGTHS

100 mg tablet. (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- QT prolongation can occur with SIRTURO. Monitor ECGs frequently. (5.2)

- Discontinue SIRTURO if significant ventricular arrhythmia or a QTcF interval > 500 ms develops. (5.2)
- Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs more frequently. (5.2)
- Hepatic-related adverse drug reactions have been reported with use of SIRTURO. Monitor liver-related laboratory tests. (5.3)
- Non-adherence to the treatment regimen could result in failure or resistance. (5.6)

ADVERSE REACTIONS

- The most common adverse reactions reported in ≥10% of patients treated with SIRTURO are nausea, arthralgia, and headache.
- Additional adverse events reported in ≥10% of patients treated with SIRTURO and with a higher frequency than the placebo treatment group are hemoptysis and chest pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Therapeutics, Division of Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid use of systemic potent CYP3A4 inducers with SIRTURO. (7.1)
- Avoid use for more than 14 consecutive days of systemic strong CYP3A4 inhibitors with SIRTURO unless the benefit outweighs the risk. Appropriate clinical monitoring for SIRTURO-related adverse reactions is recommended. (7.1)

USE IN SPECIFIC POPULATIONS

- No dosage adjustment is required in patients with mild to moderate renal impairment or in patients with mild to moderate hepatic impairment. (8.6, 8.7)
- Use with caution in patients with severe renal impairment. (8.7)
- Use with caution in patients with severe hepatic impairment and only when the benefits outweigh the risks; clinical monitoring for SIRTURO-related adverse reactions is recommended. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNINGS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Increased Mortality
- 5.2 QT Prolongation
- 5.3 Hepatic-related Adverse Drug Reactions (ADRs)
- 5.4 Drug Interactions
- 5.5 HIV-TB co-infected patients
- 5.6 Treatment failure

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience

7 DRUG INTERACTIONS

- 7.1 CYP3A4 inducers/inhibitors
- 7.2 Other Antimicrobial medications
- 7.3 Antiretroviral medications
- 7.4 QT interval Prolonging Drugs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic impairment

8.7 Renal impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamic effects
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NON-CLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

[* Sections or subsections omitted from the full prescribing information are not listed]

FULL PRESCRIBING INFORMATION

WARNINGS:

- An increased risk of death was seen in the SIRTURO™ treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.
- QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.

1 INDICATIONS AND USAGE

SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO should be administered by directly observed therapy (DOT).

This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB.

Limitations of Use:

The safety and efficacy of SIRTURO for the treatment of latent infection due to *Mycobacterium tuberculosis* has not been established. The safety and efficacy of SIRTURO for the treatment of drug-sensitive TB has not been established. In addition, there are no data on the treatment with SIRTURO of extra-pulmonary TB (e.g., central nervous system). Therefore, use of SIRTURO in these settings is not recommended.

2 DOSAGE AND ADMINISTRATION

SIRTURO should only 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 unavailable, treatment may be initiated with SIRTURO in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible.

Throughout treatment with, and following the last intake of SIRTURO, patients should continue to take their companion drugs as directed.

The recommended dosage of SIRTURO is:

- Weeks 1-2: 400 mg (4 tablets of 100 mg) once daily with food
- Weeks 3-24: 200 mg (2 tablets of 100 mg) 3 times per week with food (with at least 48 hours between doses) for a total dose of 600 mg per week.

The total duration of treatment with SIRTURO is 24 weeks. The SIRTURO tablet should be swallowed whole with water. Patients should avoid alcohol use while on treatment.

Missed doses

Patients should be advised of the need to take SIRTURO as prescribed. Compliance with the full course of therapy must be emphasized.

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From Week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen.

3 DOSAGE FORMS AND STRENGTHS

100 mg Tablet

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality

An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial (based on the 120-week visit window). One death occurred during the 24 weeks of administration of SIRTURO. The imbalance in deaths is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease could be observed. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided [*see Adverse Reactions (6.0)*].

5.2 QT Prolongation

SIRTURO prolongs the QT interval. An ECG should be obtained before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with SIRTURO. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected [*see Adverse Reactions (6.1) and Drug Interactions (7.4)*].

The following may increase the risk for QT prolongation when patients are receiving SIRTURO and therefore ECGs should be monitored closely:

- use with other QT prolonging drugs including fluoroquinolones and macrolide antibacterial drugs and the antimycobacterial drug, clofazimine

- a history of Torsade de Pointes
- a history of congenital long QT syndrome
- a history of hypothyroidism and bradyarrhythmias
- a history of uncompensated heart failure
- serum calcium, magnesium, or potassium levels below the lower limits of normal

Discontinue SIRTURO and all other QT prolonging drugs if the patient develops:

- o Clinically significant ventricular arrhythmia
- o A QTcF interval of > 500 ms (confirmed by repeat ECG)
- Monitor ECGs frequently to confirm that the QTc interval has returned to baseline.
- If syncope occurs, obtain an ECG to detect QT prolongation.

SIRTURO has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

5.3 Hepatic-related Adverse Drug Reactions (ADRs)

More hepatic-related adverse drug reactions were reported with the use of SIRTURO plus other drugs used to treat TB compared to other drugs used to treat TB without the addition of SIRTURO. Alcohol and other hepatotoxic drugs should be avoided while on SIRTURO, especially in patients with diminished hepatic reserve.

- Monitor symptoms and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed.
- An increase of serum aminotransferases to > 3xULN should be followed by repeat testing within 48 hours. Testing for viral hepatitis should be performed and other hepatotoxic medications discontinued.
- Evidence of new or worsening liver dysfunction (including clinically significant elevation of aminotransferases and/or bilirubin and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on SIRTURO should prompt additional evaluation by the prescriber.
- Discontinue SIRTURO if:
 - o aminotransferase elevations are accompanied by total bilirubin elevation > 2xULN
 - o aminotransferase elevations are > 8xULN
 - o aminotransferase elevations persist beyond 2 weeks

5.4 Drug Interactions

CYP3A4 inducers/inhibitors

Bedaquiline is metabolized by CYP3A4 and its systemic exposure and therapeutic effect may therefore be reduced during co-administration with inducers of CYP3A4. Co-administration of rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers used systemically should therefore be avoided while on treatment with SIRTURO [see *Drug Interactions (7.1)*].

Co-administration of SIRTURO with strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, the use of strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided while on SIRTURO, unless the benefit of treatment with the drug combination outweighs the risk [see *Drug Interactions (7.1)*]. Appropriate clinical monitoring for SIRTURO-related adverse reactions is recommended.

5.5 HIV-TB co-infected patients

There are no clinical data on the combined use of antiretroviral agents and SIRTURO in HIV/MDR-TB co-infected patients and only limited clinical data on the use of SIRTURO in HIV/MDR-TB co-infected patients (n=22) who were not receiving antiretroviral (ARV) therapy [see *Drug Interactions (7.3)*].

5.6 Treatment failure

SIRTURO should be administered by directly observed therapy (DOT). SIRTURO should only be administered in combination with at least 3 drugs active against the patient's TB isolate. Isolates from patients who fail to convert or relapse following treatment should be tested for bedaquiline minimum inhibitory concentrations.

6 ADVERSE REACTIONS

The most frequent adverse drug reactions (> 10.0% of patients) during treatment with SIRTURO in the controlled trials were nausea, arthralgia, and headache. Additional adverse events reported in $\geq 10\%$ of patients treated with SIRTURO and with a higher frequency than the placebo treatment group were hemoptysis and chest pain.

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Adverse drug reactions for SIRTURO were identified from the pooled safety data from 335 bedaquiline-exposed patients who received 8 weeks (Study 2) and 24 weeks (Studies 1 and 3) at the proposed dose. Studies 1 and 2 are randomized, double-blind, placebo-controlled trial in newly diagnosed patients with pulmonary MDR-TB. In both treatment arms, patients received SIRTURO or placebo in combination with other drugs used to treat MDR-TB. Study 3 is an ongoing, open-label, noncomparative study with SIRTURO administered as part of an individualized pulmonary MDR-TB treatment regimen in previously treated patients.

In Study 1 overall, 35.0% were Black, 17.5% were Hispanic, 12.5% were White, 9.4% were Asian, and 25.6% were of another race. Eight of 79 (10.1%) patients in the SIRTURO group and 16 of 81 (19.8%) patients in the placebo treatment group were HIV-infected. Seven (8.9%) SIRTURO-treated patients and six (7.4%) placebo-treated patients discontinued Study 1 because of an adverse event.

Table 1: Select Adverse Drug Reactions from Study 1 That Occurred More Frequently Than Placebo During Treatment with SIRTURO

Adverse Drug Reactions	SIRTURO Treatment Group	Placebo Treatment Group
	N=79 n (%)	N=81 n (%)
Nausea	30 (38.0)	26 (32.1)
Arthralgia	26 (32.9)	18 (22.2)
Headache	22 (27.8)	10 (12.3)
Transaminases Increased*	7 (8.9)	1 (1.2)
Blood Amylase Increased	2 (2.5)	1 (1.2)
Hemoptysis [†]	14 (17.7)	9 (11.1)
Chest Pain [†]	9 (11.4)	6 (7.4)
Anorexia [†]	7 (8.9)	3 (3.7)
Rash [†]	6 (7.6)	3 (3.7)

* Terms represented by 'transaminases increased' included transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal.

[†] Reported Adverse Events with a greater incidence in the SIRTURO treatment group but which were not identified as adverse drug reactions.

No additional unique ADRs were identified from the uncontrolled Study 3.

Deaths:

In Study 1, there was a statistically significant increased mortality risk by Week 120 in the SIRTURO treatment group compared to the placebo treatment group (9/79 (11.4%) versus 2/81 (2.5%), p-value = 0.03, an exact 95% confidence interval of the difference [1.1%, 18.2%]). Five of the 9 SIRTURO deaths and the 2 placebo deaths were TB-related. One death occurred during the 24-week SIRTURO treatment period. The median time to death for the remaining eight subjects in the SIRTURO treatment group was 329 days after last intake of SIRTURO. The imbalance in deaths is unexplained; no discernible pattern between

death and sputum conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, and severity of disease was observed.

QT Prolongation:

In Study 1, the mean increases in QTc, corrected using the Fridericia method, were greater in the SIRTURO treatment group compared to the placebo treatment group from the first week of treatment (9.9 ms at Week 1 for SIRTURO and 3.5 ms for placebo). The largest mean increase in QTc during the 24 weeks of SIRTURO treatment was 15.7 ms compared to 6.2 ms with placebo treatment (at Week 18). QT increases from baseline in the SIRTURO group persisted even after SIRTURO treatment was stopped. During the trial, there was no clear correlation of antecedent significant QT prolongation or clinically significant dysrhythmia in any of the subjects that died.

In Study 3, where patients with no treatment options received other QT-prolonging drugs used to treat TB, including clofazimine, concurrent use with SIRTURO resulted in additive QT prolongation, proportional to the number of QT prolonging drugs in the treatment regimen. Patients receiving SIRTURO alone with no other QT prolonging drug developed a mean QTcF increase over baseline of 23.7 ms with no QT segment duration in excess of 480 ms, whereas patients with at least 2 other QT prolonging drugs developed a mean QTcF prolongation of 30.7 ms over baseline, resulting in QTcF segment durations in excess of 500 ms in one patient.

There were no documented cases of Torsade de Pointes in the safety database [*see Warnings and Precautions (5.2)*].

Hepatic-Related ADRs (including abnormalities in serum transaminases):

Hepatic ADRs developed in more SIRTURO-treated patients than those treated with other drugs used to treat TB.

Laboratory tests: In both Studies 1 and 2, reversible aminotransferase elevations of at least 3xULN developed more frequently in the SIRTURO treatment group (11/102 [10.8%] vs 6/105 [5.7%] in the placebo treatment group).

Reported adverse reactions: In Study 1, increased aminotransferases were reported in 7/79 (8.9%) patients in the SIRTURO treatment group compared to 1/81 (1.2%) patients in the placebo treatment group.

7 DRUG INTERACTIONS

CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline and the formation of the major *N*-monodesmethyl metabolite (M2), which is 4 to 6-times less active in terms of antimycobacterial potency.

In vitro, bedaquiline does not significantly inhibit the activity of the following CYP450 enzymes that were tested: CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A, and it does not induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4 activities.

7.1 CYP3A4 inducers/inhibitors

Bedaquiline exposure may be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4.

Rifampin (strong CYP3A4 inducer)

In a drug interaction study of 300 mg bedaquiline and rifampin 600 mg once daily for 21 days in healthy subjects, the exposure (AUC) to bedaquiline was reduced by 52%. Due to the possibility of a reduction of the therapeutic effect of bedaquiline because of the decrease in systemic exposure, co-administration of bedaquiline and rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers used systemically should be avoided [see *Pharmacokinetics (12.3)*].

Ketoconazole (strong CYP3A4 inhibitor)

Co-administration of 400 mg bedaquiline once daily for 14 days and ketoconazole 400 mg once daily for 4 days in healthy subjects increased the exposure (AUC) to bedaquiline by 22%. Due to the potential risk of adverse reactions to bedaquiline because of the increase in systemic exposure, prolonged co-administration of bedaquiline and strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided unless the benefit outweighs the risk [see *Pharmacokinetics (12.3)*]. Appropriate clinical monitoring for SIRTURO-related adverse reactions is recommended.

7.2 Other Antimicrobial medications

The combination of 400 mg bedaquiline once daily for 14 days with isoniazid (300 mg once daily for 5 days)/pyrazinamide (1000 mg once daily for 5 days) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with SIRTURO. In a placebo-controlled clinical trial in patients with

MDR-TB, no major impact of co-administration of SIRTURO on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

7.3 Antiretroviral medications

Clinical data in HIV/MDR-TB co-infected patients on the combined use of Kaletra or nevirapine, as well as other antiretroviral agents, with SIRTURO are not available [see *Warnings and Precautions (5)*].

Kaletra (400 mg lopinavir/100 mg ritonavir)

In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and Kaletra twice daily for 24 days, exposure (AUC) to bedaquiline was increased by 22%. SIRTURO must be used with caution when co-administered with Kaletra and only if the benefit outweighs the risk [see *Warnings and Precaution (5.5)* and *Pharmacokinetics (12.3)*].

Nevirapine

Co-administration of bedaquiline 400 mg single dose and nevirapine 200 mg twice daily for 4 weeks with bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline in HIV-infected patients. No dosage adjustment of bedaquiline is required when co-administered with nevirapine [see *Pharmacokinetics (12.3)*].

7.4 QT interval Prolonging Drugs

In a drug interaction study of bedaquiline and ketoconazole, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual drugs. Additive or synergistic QT prolongation was observed when bedaquiline was co-administered with other drugs that prolong the QT interval.

In Study 3, mean increases in QTc were larger in the 17 subjects who were using clofazimine with bedaquiline at Week 24 (mean change from reference of 31.9 ms) than in subjects who were not using clofazimine with bedaquiline at Week 24 (mean change from reference of 12.3 ms) [see *Warnings and Precautions (5.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to bedaquiline. In these studies, the corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. There are, however, no adequate and well-controlled studies of SIRTURO in pregnant women. Because animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether bedaquiline or its metabolites are excreted in human milk, but rat studies have shown that drug is concentrated in breast milk.

In rats, treated with bedaquiline at doses 1 to 2 times the clinical dose (based on AUC comparisons), concentrations in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Pups from these dams showed reduced body weights compared to control animals throughout the lactation period.

Because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of SIRTURO in children and adolescents less than 18 years of age have not been established.

8.5 Geriatric Use

Clinical studies of SIRTURO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic impairment

The pharmacokinetics of bedaquiline were assessed after single-dose administration to subjects with moderate hepatic impairment (Child-Pugh B) [see *Pharmacokinetics (12.3)*]. Based on these results, no dose adjustment is necessary for SIRTURO in patients with mild or moderate hepatic impairment. SIRTURO has not been studied in patients with severe hepatic impairment and should be used with caution in these patients only when the benefits outweigh the risks. Clinical monitoring for SIRTURO-related adverse reactions is recommended [see *Warnings and Precautions (5.3)*].

8.7 Renal impairment

SIRTURO has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (< 0.001%). No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis, SIRTURO should be used with caution [see *Pharmacokinetics (12.3)*].

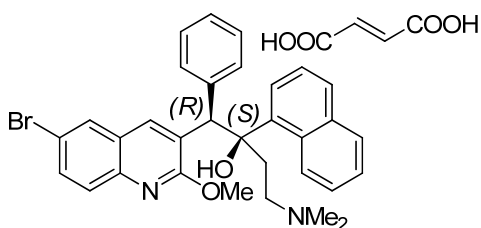
10 OVERDOSAGE

There is no experience with the treatment of acute overdose with SIRTURO. General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) should be taken in case of deliberate or accidental overdose. Removal of unabsorbed bedaquiline may be achieved by gastric lavage or aided by the administration of activated charcoal. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma.

11 DESCRIPTION

SIRTURO (bedaquiline) for oral administration is available as 100 mg strength tablets. Each tablet contains 120.89 mg of bedaquiline fumarate drug substance, which is equivalent to 100 mg of bedaquiline. Bedaquiline is a diarylquinoline antimycobacterial drug.

Bedaquiline fumarate is a white to almost white powder and is practically insoluble in aqueous media. The chemical name of bedaquiline fumarate is (1*R*, 2*S*)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol compound with fumaric acid (1:1). It has a molecular formula of $C_{32}H_{31}BrN_2O_2 \cdot C_4H_4O_4$ and a molecular weight of 671.58 (555.50 + 116.07). The molecular structure of bedaquiline fumarate is the following:



SIRTURO (bedaquiline) contains the following inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, hypromellose 2910 15 mPa.s, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, purified water (removed during processing).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bedaquiline is a diarylquinoline antimycobacterial drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamic effects

Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of *N*-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower

antimycobacterial activity (4 to 6-fold lower) compared to the parent compound. M2 concentrations appeared to correlate with QT prolongation.

12.3 Pharmacokinetics

Absorption

After oral administration bedaquiline maximum plasma concentrations ($C_{\max}$) are typically achieved at approximately 5 hours post-dose. $C_{\max}$ and the area under the plasma concentration-time curve (AUC) increased proportionally up to the highest doses studied in healthy volunteers (700 mg single-dose and once daily 400 multiple doses). Administration of bedaquiline with a standard meal containing approximately 22 grams of fat (558 total Kcal) increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. Therefore, bedaquiline should be taken with food to enhance its oral bioavailability.

Distribution

The plasma protein binding of bedaquiline is > 99.9%. The volume of distribution in the central compartment is estimated to be approximately 164 L.

Metabolism/Excretion

CYP3A4 was the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2), which is 4 to 6-times less active in terms of antimycobacterial potency. Based on preclinical studies, bedaquiline is mainly eliminated in feces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant. After reaching $C_{\max}$, bedaquiline concentrations decline tri-exponentially. The mean terminal elimination half-life of bedaquiline and the *N*-monodesmethyl metabolite (M2) is approximately 5.5 months. This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Specific Populations

Hepatic Impairment

After single-dose administration of 400 mg SIRTURO to 8 patients with moderate hepatic impairment (Child-Pugh B), mean exposure to bedaquiline and M2 (AUC_{672h}) was approximately 20% lower compared to healthy subjects. No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. SIRTURO has not been studied in patients with severe hepatic impairment and should be used with caution in these patients only when the benefits outweigh the risks. Clinical monitoring for SIRTURO-related adverse reactions is recommended [see *Warnings and Precautions* (5.3)].

Renal Impairment

SIRTURO has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial ($< 0.001\%$).

In a population pharmacokinetic analysis of MDR-TB patients treated with SIRTURO 200 mg three times per week, creatinine clearance was not found to influence the pharmacokinetic parameters of bedaquiline. It is therefore not expected that mild or moderate renal impairment will have a clinically relevant effect on the exposure to bedaquiline, and no adjustment of the bedaquiline dose is needed in patients with mild or moderate renal impairment. However, in patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis, bedaquiline should be used with caution and with increased monitoring for adverse effects, as bedaquiline concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As bedaquiline is highly bound to plasma proteins, it is unlikely that it will be significantly removed from plasma by hemodialysis or peritoneal dialysis.

Gender

In a population pharmacokinetic analysis of MDR-TB patients treated with SIRTURO no clinically relevant difference in exposure between men and women were observed.

Race

In a population pharmacokinetic analysis of MDR-TB patients treated with SIRTURO, systemic exposure (AUC) to bedaquiline was found to be 34% lower in Black patients than in patients from other race categories. This lower exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials of MDR-TB. Furthermore, response rates were comparable in patients of different race categories that completed 24 weeks of bedaquiline treatment.

HIV Co-infection

There are limited data on the use of SIRTURO in HIV co-infected patients [*see Warnings and Precautions (5) and Drug Interactions (7)*].

Geriatric Patients

There is limited data on the use of SIRTURO in TB patients 65 years and older.

In a population pharmacokinetic analysis of MDR-TB patients treated with SIRTURO, age

was not found to influence the pharmacokinetics of bedaquiline.

Pediatric Patients

The pharmacokinetics of SIRTURO in pediatric patients have not been evaluated.

Drug-Drug Interactions

Ketoconazole

Co-administration of multiple-dose bedaquiline (400 mg once daily for 14 days) and multiple-dose ketoconazole (once daily 400 mg for 4 days) in healthy subjects increased the AUC_{24h}, C_{max} and C_{min} of bedaquiline by 22% [90%CI (12; 32)], 9% [90%CI (-2, 21)] and 33% [90% CI (24, 43)] respectively. Co-administration of bedaquiline and ketoconazole or other strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided, unless the benefit of the combination of these drugs outweighs the risk. Appropriate clinical monitoring for SIRTURO-related adverse reactions is recommended.

Rifampin

In a drug interaction study of single-dose 300 mg bedaquiline and multiple-dose rifampin (once daily 600 mg for 21 days) in healthy subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. The combination of bedaquiline and rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers used systemically should be avoided.

Antimicrobial agents

The combination of multiple-dose bedaquiline 400 mg once daily with multiple-dose isoniazid/pyrazinamide (300 mg/2000 mg once daily) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose adjustment of isoniazid or pyrazinamide during co-administration with SIRTURO is required.

In a placebo-controlled study in patients with MDR-TB, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

Kaletra (400 mg lopinavir/100 mg ritonavir)

In a drug interaction study in healthy volunteers of single-dose bedaquiline (400 mg) and multiple-dose Kaletra given twice daily for 24 days, the mean AUC of bedaquiline was

increased by 22% [90% CI (11; 34)] while the mean $C_{\max}$ was not substantially affected.

Nevirapine

Co-administration of multiple-dose nevirapine 200 mg twice daily for 4 weeks in HIV-infected patients with a single 400 mg dose of bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline.

12.4 Microbiology

Mechanism of Action

Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

Mechanisms of resistance

Mycobacterial resistance mechanisms that affect bedaquiline include modification of the *atpE* target gene. Not all isolates with increased minimum inhibitory concentrations (MICs) have *atpE* mutations, suggesting the existence of at least one other mechanism of resistance.

Spectrum of Activity

Bedaquiline has been shown to be active against most isolates of *Mycobacterium tuberculosis* [see *Indications and Usage (1)* and *Clinical Studies (14)*].

Susceptibility Test Methods

In vitro susceptibility tests should be performed according to published methods^{1,2}. Based on the available information, susceptibility test interpretive criteria for bedaquiline cannot be established at this time. When susceptibility testing is performed by the 7H10 or 7H11 agar method, a range of concentrations from 0.008 microgram per mL to 1.0 microgram per mL should be assessed. The minimum inhibitory concentration (MIC) should be determined as the lowest concentration of bedaquiline that results in growth of less than or equal to 1% of the residual subpopulation. When susceptibility testing is performed by the resazurin microtiter assay (REMA) method, a range of concentrations from 0.008 microgram per mL to 1.0 microgram per mL should be assessed. The MIC should be determined as the lowest concentration of bedaquiline that prevents a visible change of resazurin color from blue to pink. All assays should be performed in polystyrene plates or tubes. Löwenstein-Jensen (LJ) medium should not be used.

The actual MIC should be reported. A specialist in drug-resistant TB should be consulted in evaluating therapeutic options.

The bedaquiline agar (left) and REMA (right) MIC distributions against clinical isolates resistant to isoniazid and rifampin from Studies 1, 2, and 3 are provided below.

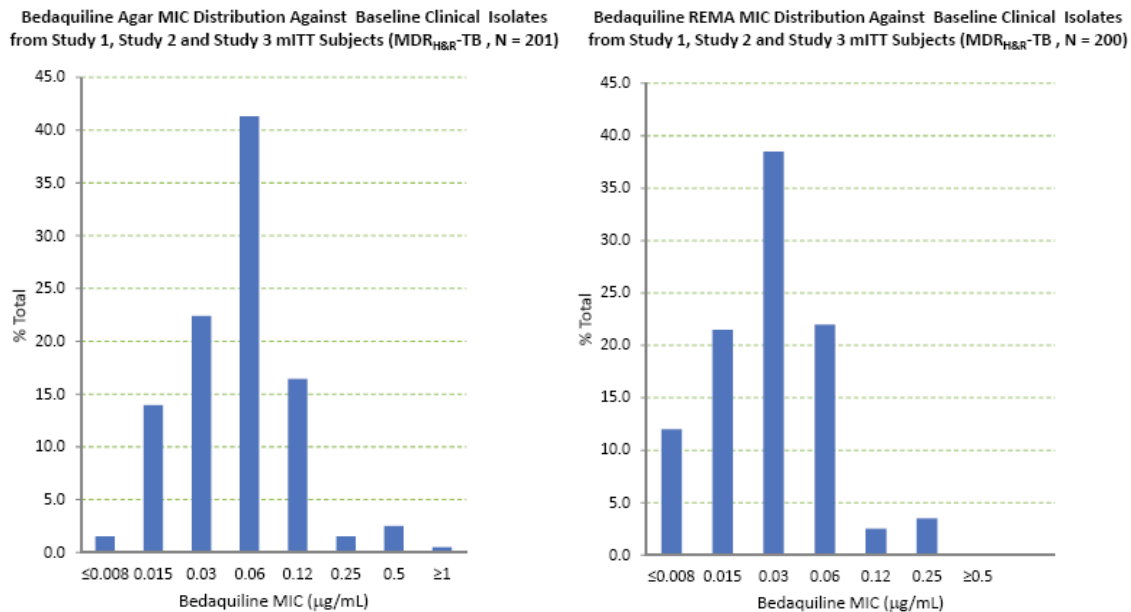


Figure 1: Bedaquiline MIC Distribution against Baseline MDR_{H&R}-TB Isolates from Studies 1, 2, and 3 mITT Subjects: Agar Method (left) and REMA Method (right)

MICs for baseline *M. tuberculosis* isolates from subjects in Studies 1 and 3 and their sputum culture conversion rates at Week 24 are shown in Table 2 below. No correlation was seen between the culture conversion rates at Week 24 and baseline MICs.

Table 2. Culture Conversion Rates (Week 24 Data Selection, No Overruling for Discontinuation) at Week 24 By Baseline Bedaquiline MIC for mITT Subjects from Study 1 and Study 3

Baseline Bedaquiline MIC (micrograms/mL)	SIRTURO (Bedaquiline) Treatment Group	
	24-Week Culture Conversion Rate	
	n/N (%)	
	7H11 Agar	REMA
≤ 0.008	2/2 (100)	21/25 (84.0)
0.015	15/18 (83.3)	33/39 (84.6)
0.03	40/49 (81.6)	70/92 (76.1)
0.06	80/105 (76.2)	45/56 (80.4)
0.12	35/41 (85.4)	6/7 (85.7)
0.25	1/2 (50.0)	3/4 (75.0)

0.5	4/5 (80.0)	0/1 (0)
≥ 1	0/1 (0)	

N = number of subjects with data; *n* = number of subjects with that result; MIC = minimum inhibitory concentration; BR = background regimen

In SIRTURO-treated patients from Studies 1, 2, and 3, with at least a four-fold increase in bedaquiline MIC from baseline and with *atp* operon sequencing results, no coding variation in the *atp* operon was seen, suggesting a mechanism of resistance other than mutations in the *atpE* gene. Of these subjects for the agar method, patients who experienced failure to convert their sputum or relapsed (n=9) had post-baseline isolates with 4-fold to greater than 8-fold increases in MIC (corresponding to post-baseline MICs of 0.24 to greater than 0.48 microgram/mL). For the REMA method, patients who experienced failure or relapsed had post-baseline isolates with 4-fold to greater than 16-fold increases in MIC (corresponding to post-baseline MICs of 0.015 to 1.0 microgram/mL). All 9 subjects with increased MICs and failure or relapse were infected with MDR-TB isolates that were resistant to additional antimycobacterial drugs in their treatment regimen.

Quality Control

Susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of testing. Assays using standard bedaquiline powder should provide the following range of MIC values shown in Table 3.

Table 3. Quality Control Ranges using Agar and REMA Methods and *M. tuberculosis* H37Rv

Organism	Bedaquiline MIC (micrograms/mL)	
	Agar	REMA
<i>M. tuberculosis</i> H37Rv	0.03 – 0.12	0.03 – 0.12

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

No mutagenic or clastogenic effects were detected in the *in vitro* non-mammalian reverse mutation (Ames) test, *in vitro* mammalian (mouse lymphoma) forward mutation assay and an *in vivo* mouse bone marrow micronucleus assay.

SIRTURO had no effects on fertility when evaluated in male and female rats. No relevant drug-related effects on developmental toxicity parameters were observed in rats and rabbits. The corresponding plasma exposure (AUC) was 2-fold higher in rats and lower for rabbits compared to humans. There was no effect of maternal treatment with bedaquiline at any

dose level on sexual maturation, behavioral development, mating performance, fertility or reproductive capacity of the F1 generation animals. Body weight decreases in pups were noted in high dose groups during the lactation period after exposure to bedaquiline via milk and were not a consequence of in utero exposure. Concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma.

13.2 Animal Toxicology and/or Pharmacology

Bedaquiline is a cationic, amphiphilic drug that induced phospholipidosis (at almost all doses, even after very short exposures) in drug-treated animals, mainly in cells of the monocytic phagocytic system (MPS). All species tested showed drug-related increases in pigment-laden and/or foamy macrophages, mostly in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas and/or uterus. After treatment ended, these findings were slowly reversible. Muscle degeneration was observed in several species at the highest doses tested. For example the diaphragm, esophagus, quadriceps and tongue of rats were affected after 26 weeks of treatment at doses similar to clinical exposures based on AUC comparisons. These findings were not seen after a 12-week, treatment-free, recovery period and were not present in rats given the same dose biweekly. Degeneration of the fundic mucosa of the stomach, hepatocellular hypertrophy and pancreatitis were also seen.

14 CLINICAL STUDIES

A placebo-controlled, double-blind, randomized trial (Study 1) was conducted in newly diagnosed patients with multi-drug resistant pulmonary *Mycobacterium tuberculosis*. Patients were randomized to receive treatment with either SIRTURO and other drugs used to treat MDR-TB (SIRTURO treatment group) (n=79) or placebo plus other drugs used to treat MDR-TB (placebo treatment group) (n=81); the other drugs used to treat MDR-TB consisted of a combination of 5 other antimycobacterial drugs (ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative). Sixty-three percent of the population was male, with a median age of 34 years, 35% were Black, and 15% were HIV-positive. Most patients had cavitation in one lung (62%); cavitation in both lungs was observed in 18% of patients.

SIRTURO was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times per week for the following 22 weeks. After the 24-week study drug (SIRTURO or placebo) treatment phase, patients continued to receive their other drugs used to treat MDR-TB until a total treatment duration of 18 to 24 months was achieved, or at least 12 months after the first confirmed negative culture.

Time to sputum culture conversion was defined as the interval in days between the first dose of study drug and the date of the first of two consecutive negative sputum cultures collected

at least 25 days apart during treatment. In this ongoing trial, the SIRTURO treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 24. Median time to culture conversion was 83 days for the SIRTURO treatment group compared to 125 days for the placebo treatment group. Table 4 shows the proportion of patients with sputum culture conversion after 24 weeks and 72 weeks of treatment with SIRTURO or placebo in combination with other drugs used to treat MDR-TB (with patients who discontinued or died considered as failures).

Table 4: Culture Conversion Status at Week 24 and Week 72 in Study 1

Microbiologic Status	SIRTURO Treatment Group N = 67 n (%)	Placebo Treatment Group N = 66 n (%)	Difference [95% CI] p-value
Week 24			
Treatment success	52 (77.6%)	38 (57.6%)	20.0% [4.5%, 35.6%] 0.014
Treatment failure	15 (22.4%)	28 (42.4%)	
Lack of conversion	5 (7.5%)	16 (24.2%)	
Discontinuation	10 (14.9%)	12 (18.2%)	
Week 72			
Treatment success	47 (70.1%)	37 (56.1%)	14.1% [-2.1%, 30.3%] 0.092
Treatment failure	20 (29.9%)	29 (43.9%)	
Lack of conversion	3 (4.5%)	7 (10.6%)	
Discontinuation	17 (25.4%)	22 (33.3%)	

Study 2 was a smaller placebo controlled study designed similarly to Study 1 except that SIRTURO or placebo was given for only 8 weeks instead of 24 weeks. Patients were randomized to either SIRTURO and other drugs used to treat MDR-TB (SIRTURO treatment group) (n=23) or placebo and other drugs used to treat MDR-TB (placebo treatment group) (n=24). Twenty-one patients randomized to the SIRTURO treatment group and 23 patients randomized to the placebo treatment group had confirmed MDR-TB based on subjects' baseline *M. tuberculosis* isolate obtained prior to randomization. The SIRTURO treatment group had a decreased time to culture conversion and improved culture conversion rates compared to the placebo treatment group at Week 8. At Weeks 8 and 24, the differences in culture conversion proportions were 38.9% (95% CI: [12.3%, 63.1%] and p-value: 0.004), 15.7% (95% CI: [-11.9%, 41.9%] and p-value: 0.32), respectively.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Susceptibility Testing of Mycobacteria, Nocardaceae, and other Aerobic Actinomycetes; Approved Standard – 2nd ed. CLSI document M24-A2. CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA, 19087, 2011.

2. Martin A, Portaels F, Palomino JC. Colorimetric redox-indicator methods for the rapid detection of multidrug resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. J Antimicrob Chemother. 2007; 59 (2): 175-83.

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied

SIRTURO is supplied as uncoated white to almost white round biconvex 100 mg tablets with debossing of "T" over "207" on one side and "100" on the other side. The tablets are packaged in white high density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closure with induction seal liner. Each bottle contains 188 tablets.

NDC 59676-701-01

Storage and handling

Keep out of reach of children.

Dispense in original container. Tablets dispensed outside the original container should be stored in a tight light-resistant container with an expiration date not to exceed 3 months.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

Tuberculosis is a serious disease that can be fatal; some patients with resistant TB may have limited treatment options. Patients should be advised that the following serious side effects can occur with SIRTURO: death, heart rhythm abnormalities, and/or hepatitis. In addition, patients should also be advised about other potential side effects: nausea, joint pain, headache, increased blood amylase, hemoptysis, chest pain, anorexia, and/or rash. Additional testing may be needed to monitor or reduce the likelihood of adverse effects.

Take SIRTURO in combination with other antimycobacterial drugs as prescribed. Compliance with the full course of therapy must be emphasized. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the treatment and (2) increase the likelihood that their mycobacterium may develop resistance and the disease will not be treatable by SIRTURO or other antibacterial drugs in the future.

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From Week 3 onwards, if a

200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen.

Patients should be informed to take SIRTURO with food.

Patients should be advised to abstain from alcohol, hepatotoxic medications or herbal products.

Patients should be advised to discuss with their physician the other medications they are taking and other medical conditions before starting treatment with SIRTURO.

Patients should be advised to consult with their doctor if they have a personal or family history of congenital QT prolongation or heart failure.

Product of Switzerland

Finished Product Manufactured by: Kemwell Pvt. Ltd., Bangalore, India

Manufactured for:

Janssen Therapeutics, Division of Janssen Products, LP
Titusville, NJ 08560

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MEDICATION GUIDE
SIRTURO™ (ser toor' oh)
(bedaquiline)
TABLETS

Read this Medication Guide before you start taking SIRTURO™ and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SIRTURO™?

SIRTURO™ is an antibiotic prescription medicine used to treat multi-drug resistant tuberculosis (TB) of the lungs in people with limited treatment options. Multi-drug resistant tuberculosis is a serious disease that can result in death and for which there are few treatment choices. More people treated with SIRTURO™ cleared TB from their sputum compared to people who did not receive SIRTURO™.

It is important to complete the full course of treatment with SIRTURO™ and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by SIRTURO™ or other medicines.

SIRTURO™ can cause serious side effects.

- In one clinical trial, more deaths were seen in people who were treated with SIRTURO™ compared to people who did not receive SIRTURO™.
- Heart rhythm problems can happen with SIRTURO™.
- Talk with your healthcare provider about whether SIRTURO™ is right for you.

WHAT IS SIRTURO™?

SIRTURO™ is an antibiotic prescription medicine used to treat resistant tuberculosis (TB) of the lungs.

It is not known if SIRTURO™ is safe and effective in:

- people who do not have active TB
- people who have TB that is not resistant to antibiotics
- people who have types of TB other than TB of the lungs
- children under 18 years of age

Before you take SIRTURO™, tell your healthcare provider if you:

- have had an abnormal heart rhythm (ECG) or other heart problems.

- anyone in your family has or has had a heart problem called “congenital long QT syndrome”.
- have liver or kidney problems or any other medical conditions, including HIV infection.
- are pregnant or plan to become pregnant. It is not known if SIRTURO™ will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SIRTURO™ passes into breast milk. You and your healthcare provider should decide if you will take SIRTURO™ or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

HOW SHOULD I TAKE SIRTURO™?

- SIRTURO™ must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with SIRTURO™.
- Take SIRTURO™ with food. Swallow the tablets whole with water.
- Take SIRTURO™ exactly as your healthcare provider tells you to take it. Take SIRTURO™ for a total of 24 weeks.

Week 1 and Week 2:

Take 400 mg (4 tablets) **1 time each day.**

Week 3 to Week 24:

- Take 200 mg (2 tablets) a day 3 times a week.
- For example, you may take SIRTURO™ on Monday, Wednesday and Friday every week.
- **Do not** take more than 600 mg (6 tablets) SIRTURO™ during a 7 day period.
- You may need to take your other TB medicines for longer than 24 weeks. Check with your healthcare provider.
- **Do not skip SIRTURO™ doses. If you skip doses,** or do not complete the total 24 weeks of SIRTURO™ your treatment may not work as well and your TB may be harder to treat.
- If you take more SIRTURO™ than you should, talk to a healthcare provider right away.
- **If you miss your SIRTURO™ dose during Week 1 or Week 2:**
 - **Do not** take a double dose to make up for the missed dose. Take the next dose as usual.

If you miss your SIRTURO™ dose during Week 3 to Week 24:

- Take the missed dose as soon as possible and resume the three times a week schedule.
- **Do not** take more than 600 mg (6 tablets) in total during a 7 day period. You should take 2 tablets per day, three times a week.

If you miss a dose and you are not sure what to do, talk to your healthcare provider.

- **Do not** stop taking SIRTURO™ without first talking to your healthcare provider.

WHAT SHOULD I AVOID WHILE TAKING SIRTURO™?

- You should not drink alcohol while taking SIRTURO™.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF SIRTURO™?

SIRTURO™ may cause serious side effects, including:

- See “What is the most important information I should know about SIRTURO™?”
- **serious heart rhythm changes (QT prolongation).** Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint.
- **liver problems (hepatotoxicity).** Call your healthcare provider right away if you have unexplained symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light colored bowel movements, dark colored urine, yellowing of your skin or the white of your eyes.

Side effects of SIRTURO™ include nausea, joint pain, headache, an abnormal lab test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash.

These are not all the possible side effects of SIRTURO™. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

HOW SHOULD I STORE SIRTURO™?

- Store SIRTURO™ at 77°F (25°C).
- Keep SIRTURO™ in the original container, and keep SIRTURO™ out of light.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF SIRTURO™.

- This Medication Guide summarizes the most important information about SIRTURO™. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about SIRTURO™ that is written for health professionals.

WHAT ARE THE INGREDIENTS IN SIRTURO™?

Active ingredient: bedaquiline.

Inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate, cornstarch, microcrystalline cellulose, polysorbate 20, purified water (removed during processing).

Product of Switzerland

Finished Product Manufactured by: Kemwell Pvt. Ltd., Bangalore, India

Manufactured for: Janssen Therapeutics, Division of Janssen Products, LP Titusville, NJ 08560
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This Medication Guide has been approved by the U.S. Food and Drug Administration

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