

เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

SIRTURO®

FULL PRESCRIBING INFORMATION

WARNING: QTc PROLONGATION

QTc prolongation can occur with SIRTURO. Use with drugs that prolong the QTc interval may cause additive QTc prolongation. Monitor ECGs. Discontinue SIRTURO if significant ventricular arrhythmia or QTc interval greater than 500 ms develops [see *Special warning and precautions for use (4.4.1)*].

1. Name of the Medicinal Product

1.1 Product Name

SIRTURO®

1.2 Strength

100 mg

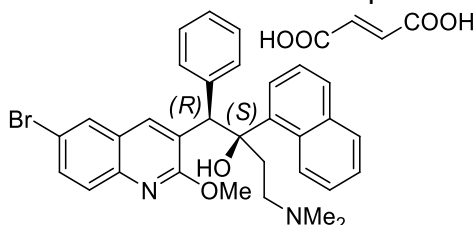
1.3 Pharmaceutical Dosage Form

Tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

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).

2.2 Quantitative Declaration

SIRTURO (bedaquiline) is a diarylquinoline antimycobacterial drug containing bedaquiline as the fumarate salt. SIRTURO is available as 100 mg strength tablets for oral administration. Each tablet contains 100 mg of bedaquiline (equivalent to 120.89 mg of bedaquiline fumarate).

3. Pharmaceutical Form

SIRTURO tablets, 100 mg are uncoated white to almost white round biconvex with debossing of "T" over "207" on one side and "100" on the other side.

4. Clinical Particulars

4.1 Therapeutic indication

SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (12 to less than 18 years of age and weighing at least 30 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampin and isoniazid.

Limitations of Use:

- Do not use SIRTURO for the treatment of:
 - Latent infection due to *Mycobacterium tuberculosis* (*M. tuberculosis*)
 - Drug-sensitive pulmonary TB
 - Extra-pulmonary TB
 - Infections caused by non-tuberculous mycobacteria

4.2 Posology and method of administration

4.2.1 Important Administration Instructions

- Administer SIRTURO by directly observed therapy (DOT).
- Only use SIRTURO in combination with at least three other drugs to which the patient's TB isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, SIRTURO treatment may be initiated in combination with at least four other drugs to which the patient's TB isolate is likely to be susceptible. Refer to the prescribing information of the drugs used in combination with SIRTURO for further information.
- SIRTURO must be taken with food.
- Emphasize the need for compliance with the full course of therapy.

4.2.2 Required Testing Prior to Administration

Prior to treatment with SIRTURO, obtain the following:

- Susceptibility information for the background regimen against *M. tuberculosis* isolate if possible [*see Posology and method of administration (4.2.1)*]
- ECG [*see Special Warnings and Precautions for use (4.4.1)*]
- Serum potassium, calcium, and magnesium concentrations [*see Special Warnings and Precautions for use (4.4.1)*]
- Liver enzymes [*see Special Warnings and Precautions for use (4.4.4)*]

4.2.3 Recommended Dosage in Combination Therapy

The recommended dosage of SIRTURO is:

Table 1: Recommended Dosage of SIRTURO

Population	Dosage
Adult patients (18 years of age and older)	400 mg orally once daily for the first two weeks, followed by 200 mg orally three times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks)
Pediatric patients (12 to less than 18 years of age) and weighing at least 30 kg	

The SIRTURO tablet should be swallowed whole with water and taken with food. The total duration of treatment with SIRTURO is 24 weeks. When treatment with SIRTURO is considered necessary beyond 24 weeks in patients 16 years and older, and weighing at least 30 kg, treatment may be continued at a dose of 200 mg three times per week [see *Clinical studies*].

4.2.4 Missed Dose

If a dose is missed during the first 2 weeks of treatment, do not administer the missed dose (skip the dose and then continue the daily dosing regimen). From Week 3 onwards, if a 200 mg dose is missed, administer the missed dose as soon as possible, and then resume the 3 times a week dosing regimen. The total dose of SIRTURO during a 7-day period should not exceed the recommended weekly dose (with at least 24 hours between each intake).

4.2.5 Pediatric Use

The safety and effectiveness of SIRTURO have been established in pediatric patients 12 to less than 18 years of age and weighing at least 30 kg. The use of SIRTURO in this pediatric population is supported by evidence from the study of SIRTURO in adults together with additional pharmacokinetic and safety data from the single-arm, open-label, trial that enrolled 15 pediatric patients 14 to less than 18 years of age with confirmed or probable pulmonary TB caused by *M. tuberculosis* resistant to at least rifampin who were treated with SIRTURO for 24 weeks in combination with a background regimen [see *Undesirable effects (4.8)*, *Pharmacokinetic Properties (5.2)* and *Clinical Studies*]. The use of SIRTURO in pediatric patients 12 to less than 14 years of age is based on information obtained from the studies conducted in adults and pediatric patients 14 to less than 18 years of age [see *Undesirable effects (4.8)* and *Clinical Studies*].

The safety and effectiveness of SIRTURO in pediatric patients less than 12 years of age and/or weighing less than 30 kg have not been established.

4.2.6 Geriatric Use

Clinical studies of SIRTURO did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients [see *Pharmacological Properties (5.2)*].

4.2.7 Hepatic Impairment

The pharmacokinetics of bedaquiline were assessed after single-dose administration to adult patients with moderate hepatic impairment (Child-Pugh B) [see *Pharmacokinetic Properties (5.2)*]. 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 *Special Warnings and Precautions for use (4.4.4)*].

4.2.8 Renal Impairment

SIRTURO has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (less than or equal to 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 *Pharmacokinetic Properties (5.2)*]. Monitor adult and pediatric patients for adverse reactions of SIRTURO when administered to patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

4.3 Contraindication

None

4.4 Special warning and precautions for use

4.4.1 QTc Prolongation

SIRTURO prolongs the QTc interval [see *Pharmacological Properties (5.1)*]. Use with drugs that prolong the QTc interval may cause additive QTc prolongation [see *Undesirable effects (4.8)*]. In Study 4, where SIRTURO was administered with the QTc prolonging drugs clofazimine and levofloxacin, 5% of patients in the 40-week SIRTURO treatment group experienced a QTc ≥ 500 ms and 43% of patients experienced an increase in QTc ≥ 60 ms over baseline. Of the clofazimine- and levofloxacin-treated patients in the 40-week control arm, 7% of patients experienced a QTc ≥ 500 ms and 39% experienced an increase in QTc ≥ 60 ms over baseline.

Obtain an ECG before initiation of treatment, 2 weeks after initiation, during treatment, as clinically indicated and at the expected time of maximum increase in the QTc interval of the concomitantly administered QTc prolonging drugs (as applicable). Obtain electrolytes at baseline and during treatment and correct electrolytes as clinically indicated.

The following may increase the risk for QTc prolongation when patients are taking SIRTURO:

- use with other QTc prolonging drugs
- a history of Torsade de Pointes

- a history of congenital long QTc syndrome
- a history of or ongoing hypothyroidism
- a history of or ongoing bradyarrhythmias
- a history of uncompensated heart failure
- serum calcium, magnesium, or potassium levels below the lower limits of normal

Discontinue SIRTURO if the patient develops:

- Clinically significant ventricular arrhythmia
- A QTc interval of greater than 500 ms (confirmed by repeat ECG)

If syncope occurs, obtain an ECG to detect QTc prolongation.

4.4.2 Mortality Imbalance in Clinical Trials

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 in adults (Study 1; 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 tuberculosis, HIV status, or severity of disease could be observed. In a subsequent active-controlled trial in adults (Study 4), deaths by Week 132 occurred in 11/211 (5.2%) patients in the 40-week SIRTURO treatment group, 8/202 (4%) patients in the active-control treatment group including four of 29 patients who received SIRTURO as part of a salvage treatment, and 2/143 (1.4%) patients in the 28-week SIRTURO treatment group [*see Undesirable effects (4.8)*].

4.4.3 Risk of Development of Resistance to Bedaquiline

A potential for development of resistance to bedaquiline in *M. tuberculosis* exists [*see Microbiology*]. Bedaquiline must only be used in an appropriate combination regimen for the treatment of pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid, to reduce the risk of development of resistance to bedaquiline [*see Therapeutic indication (4.1)*].

4.4.4 Hepatotoxicity

In clinical trials, more hepatic-related adverse reactions were reported in adults 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 impaired hepatic function. Hepatic-related adverse reactions have also been reported in pediatric patients 14 to less than 18 years of age [*see Undesirable effects (4.8.1)*].

Monitor symptoms (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed. Test for viral hepatitis and discontinue other hepatotoxic medications if evidence of new or worsening liver dysfunction occurs. Discontinue SIRTURO if:

- transaminase elevations are accompanied by total bilirubin elevation greater than two times the upper limit of normal

- transaminase elevations are greater than eight times the upper limit of normal
- transaminase elevations are greater than five times the upper limit of normal and persist beyond two weeks

4.4.5 Drug Interactions

CYP3A4 Inducers

Coadministration of SIRTURO with a moderate or strong CYP3A4 inducer decreases the systemic exposure of bedaquiline and may reduce the therapeutic effect of SIRTURO. Avoid coadministration of SIRTURO with moderate or strong CYP3A4 inducers, such as efavirenz and rifamycins (i.e., rifampin, rifapentine and rifabutin) [*see Interaction with other medicinal products and other forms of interactions (4.5.1)*].

CYP3A4 Inhibitors

Coadministration of SIRTURO with CYP3A4 inhibitors increases the systemic exposure of bedaquiline, which may increase the risk of adverse reactions. Closely monitor patient safety (e.g., liver function) when SIRTURO is coadministered with CYP3A4 inhibitors [*see Interaction with other medicinal products and other forms of interactions (4.5.1)*].

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effect of Other Drugs on SIRTURO

Strong and Moderate CYP3A4 Inducers

Coadministration of SIRTURO with moderate or strong CYP3A4 inducers may decrease systemic exposure of bedaquiline. Avoid coadministration of SIRTURO with strong or moderate CYP3A4 inducers [*see Pharmacokinetic Properties (5.2)*].

CYP3A4 Inhibitors

Coadministration of SIRTURO with CYP3A4 inhibitors increases the systemic exposure of bedaquiline which may increase the risk of adverse reactions. Closely monitor patient safety (e.g., liver function) when SIRTURO is coadministered with CYP3A4 inhibitors. No dose adjustment of SIRTURO is needed when coadministered with CYP3A4 inhibitors [*see Pharmacokinetic Properties (5.2)*].

4.5.2 Other Antimicrobial Medications

No dose adjustment of isoniazid or pyrazinamide is required during coadministration with SIRTURO.

In a placebo-controlled clinical trial in adult patients, no major impact of co-administration of SIRTURO on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

4.5.3 QTc Interval Prolonging Drugs

In clinical trials of adult patients, additional QTc interval prolongation was observed during combination treatment with SIRTURO and other QTc prolonging drugs.

In Study 3, concurrent use of clofazimine with SIRTURO resulted in QTc prolongation: mean increases in QTc were larger in the 17 adult patients who were taking clofazimine with bedaquiline at Week 24 (mean change from Day-1 of 32 ms) than in patients who were not taking clofazimine with bedaquiline at Week 24 (mean change from Day-1 of 12 ms). Monitor ECGs if SIRTURO is co-administered to patients receiving other drugs that prolong the QTc interval, and discontinue SIRTURO if there is evidence of serious ventricular arrhythmia or QTc interval greater than 500 ms. [see *Special Warnings and Precautions for use (4.4.1) and Pharmacodynamic Properties (5.1)*]. ECG monitoring should be performed prior to initiation and at the expected time of maximum increase in the QTc interval of the concomitantly administered QTc prolonging drugs.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

Available data from published literature of SIRTURO use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks associated with active TB during pregnancy (see *Clinical Considerations*).

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oral administration of bedaquiline to pregnant rats and rabbits during organogenesis at exposures up to 6 times the clinical dose based on AUC comparisons (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Active TB in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, caesarean delivery, preterm birth, low birth weight, birth asphyxia, and perinatal infant death.

Data

Animal Data

Pregnant rats were treated with bedaquiline at 5, 15 and 45 mg/kg (approximately 0.7, 2 and 6 times the clinical dose based on AUC comparisons) during the period of

organogenesis (gestational Days 6 to 17, inclusive). Pregnant rabbits were treated with bedaquiline at 10, 30 and 100 mg/kg (approximately 0.05, 0.2 and 1.5 times the clinical dose based on AUC comparisons) during the period of organogenesis (gestational Days 6 to 19, inclusive). No embryotoxic effects were found in rats or rabbits at dose exposures up to 6 times the clinical dose exposures based on AUC comparisons.

4.6.2 Lactation

Risk Summary

Data from a published clinical lactation study demonstrate higher bedaquiline concentrations in breast milk compared to maternal plasma, suggesting that bedaquiline accumulates in breast milk (see Data). Data are insufficient to determine effects of the drug on the breastfed infants. No data are available on the effects of the drug on milk production. Because of the potential for serious adverse reactions in a breastfed infant, including hepatotoxicity, advise patients that breastfeeding is not recommended during treatment with SIRTURO and for 27.5 months (5 times the half-life) after the last dose unless infant formula is not available.

Clinical Considerations

If an infant is exposed to bedaquiline through breast milk, monitor for signs of bedaquiline-related adverse reactions, such as hepatotoxicity [*see Undesirable effects (4.8)*].

Data

A clinical lactation study was conducted in two lactating women who were approximately 7 weeks' postpartum. Bedaquiline and M2, its active metabolite, levels were measured between approximately 27 and 48 hours after the last bedaquiline dose, and concentrations of bedaquiline and M2 ranged from 2.61 to 8.11 mg/L and 0.27 to 0.81 mg/L, respectively. The milk:plasma ratios for bedaquiline and M2 at 27 to 48 hours after the last dose of bedaquiline ranged from approximately 19 to 29 and 4 to 6, respectively.

4.7 Effect on ability to drive and use machine

Adverse reactions, such as dizziness, may affect the ability to drive or use machines, although no studies on this effect with bedaquiline have been performed. Patients should be advised not to drive or operate machinery if they experience dizziness while taking SIRTURO.

4.8 Undesirable effects

The following serious adverse reactions are discussed elsewhere in the labeling:

- QTc Prolongation [*see Special Warnings and Precautions for use (4.4.1)* and *Pharmacodynamic Properties (5.1)*]
- Mortality Imbalance in Clinical Trials [*see Special Warnings and Precautions for use (4.4.2)*]
- Hepatotoxicity [*see Special Warnings and Precautions for use (4.4.4)*]
- Drug Interactions [*see Special Warnings and Precautions for use (4.4.5)*]

4.8.1 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. Refer to the prescribing information of the drugs used in combination with SIRTURO for their respective adverse reactions.

Clinical Studies Experience in Adults

Adverse reactions for SIRTURO were identified from safety data from 335 patients who received SIRTURO for eight weeks (Study 2) and 24 weeks (Studies 1 and 3) , and 354 patients who received SIRTURO for 40 weeks or 28 weeks (Study 4). In these studies, patients received SIRTURO in combination with other antimycobacterial drugs.

Studies 1 and 2 were randomized, double-blind, placebo-controlled trials in newly diagnosed patients with pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid. Study 3 was an open-label, noncomparative study with SIRTURO administered as part of an individualized treatment regimen in previously treated patients with pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid, including patients resistant to second-line injectables and/or fluoroquinolones.

In Study 1, 35% were Black, 17% were Hispanic, 13% were White, 9% were Asian, and 26% were of another race. Eight of 79 (10%) patients in the SIRTURO group and 16 of 81 (20%) 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 reaction.

Study 4 was an open-label, randomized, active-controlled trial in patients with pulmonary TB due to *M. tuberculosis* resistant to at least rifampin that evaluated a 40-week arm of SIRTURO in combination with other oral antimycobacterial drugs compared with a 40-week active control arm that included an injectable antimycobacterial drug in combination with other oral antimycobacterial drugs. A 28-week arm including SIRTURO, an injectable and other antimycobacterial drugs, was also evaluated in the trial, but recruitment was stopped early due to changes in the standard of care. In the population treated in the two 40-week arms (N=413), the median age was 32.8 years, 61% were male, 46% were Asian, 36% were Black, 18% were White and 16% were HIV infected.

Common Adverse Reactions

Table 2 presents select adverse reactions that occurred more frequently in the SIRTURO arm than the placebo arm in Study 1. The most common adverse reactions reported in 10% or more patients treated with SIRTURO and occurred more frequently than the placebo arm were nausea, arthralgia, headache, hemoptysis and chest pain.

Table 2: Select Adverse Reactions from Study 1 that Occurred More Frequently than Placebo During Treatment with SIRTURO

Adverse Reactions	SIRTURO Treatment	Placebo Treatment
	Group N=79 n (%)	Group N=81 n (%)
Nausea	30 (38)	26 (32)
Arthralgia	26 (33)	18 (22)
Headache	22 (28)	10 (12)
Hemoptysis	14 (18)	9 (11)
Chest Pain	9 (11)	6 (7)
Anorexia	7 (9)	3 (4)
Transaminases Increased*	7 (9)	1 (1)
Rash	6 (8)	3 (4)
Blood Amylase Increased	2 (3)	1 (1)

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

No additional unique adverse reactions were identified from the uncontrolled Study 3.

Transaminase Elevations

In both Studies 1 and 2, transaminase elevations of at least 3 times the upper limit of normal developed more frequently in the SIRTURO treatment group (11/102 [10.8%] vs 6/105 [5.7%]) than in the placebo treatment group. In Study 3, 22/230 (9.6%) patients had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than or equal to 3 times the upper limit of normal during the overall treatment period.

In Study 4 during the treatment phase, transaminase elevations of at least 3 times the upper limit of normal developed in 45/211 (21%) in the 40-week SIRTURO treatment group, 45/202 (22%) in the 40-week active comparator group, and 23 /143 (16%) in the 28-week SIRTURO-containing group.

Table 3 presents select adverse reactions occurring in 5% or greater of patients receiving SIRTURO in combination with other antimycobacterial drugs in the 40-week SIRTURO arm in Study 4. The most common adverse reactions reported in 10% or more patients in the 40-week SIRTURO arm were QTc prolongation, nausea, vomiting, arthralgia, transaminases increased, abdominal pain, pruritus, dizziness, headache, chest pain, rash, insomnia, dry skin, and palpitations.

Table 3: Select Adverse Reactions Occurring in 5% or Greater of Patients Receiving the 40-Week SIRTURO Regimen in Study 4

Adverse Reactions	SIRTURO ^a N=211 n (%)	Active Control ^{b,c} N=202 n (%)
QTc prolongation	128 (61)	113 (56)
Nausea	114 (54)	126 (62)
Vomiting	112 (53)	125 (62)
Arthralgia	93 (44)	67 (33)
Transaminases increased ^d	63 (30)	59 (29)
Abdominal pain ^e	60 (28)	48 (24)

Pruritus ^f	58 (27)	44 (22)
Dizziness	37 (18)	42 (21)
Headache	36 (17)	36 (18)
Chest pain	33 (16)	24 (12)
Rash ^g	30 (14)	17 (8)
Insomnia	30 (14)	19 (9)
Dry skin	25 (12)	16 (8)
Palpitations	21 (10)	13 (6)
Myalgia	19 (9)	6 (3)
Paresthesia	16 (8)	8 (4)
Diarrhea	12 (6)	17 (8)

^a 40-week, bedaquiline, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase).

^b 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high dose isoniazid and prothionamide in the first 16 weeks (intensive phase).

^c Study 4 was not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the SIRTURO and the active control treatment groups.

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

^e Terms represented by 'abdominal pain' included abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal tenderness.

^f Terms represented by 'pruritus' included pruritus, pruritus generalized, and rash pruritic.

^g Terms represented by 'rash' included rash, rash papular and rash maculopapular.

In the 28-week SIRTURO-containing arm (N=143), in which SIRTURO was used in combination with other antimycobacterial drugs, the most common selected adverse reactions (greater than 10%) were QTc prolongation (56%), arthralgia (55%), nausea (43%), vomiting (29%), pruritus (25%), transaminases increased (21%), dizziness (21%), chest pain (17%), abdominal pain (17%), headache (16%), rash (12%), and hemoptysis (11%).

Mortality Imbalance in Clinical Studies

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 patients 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.

In the open-label Study 3, 16/233 (6.9%) patients died. The most common cause of death as reported by the investigator was TB (nine patients).

In Study 4, patients originally assigned to non-SIRTURO containing regimens could receive SIRTURO as salvage when the original therapy was not tolerated or ineffective. At Week 132, deaths were observed in 11/211 (5.2%) patients in the 40-week SIRTURO arm versus

8/202 (4.0%) patients in the 40-week active control arm. For the 40-week SIRTURO arm, the most common cause of death was related to TB (five patients). In the 40-week active control arm, which included four of 29 patients who received SIRTURO as part of a salvage treatment, the most common cause of death was related to respiratory disease (e.g., TB, lobar pneumonia, respiratory distress in an HIV-positive patient). The adjusted difference in proportion of fatal adverse reactions between the 40-week SIRTURO arm and the 40-week active control arm was 1.2% [95% CI (-2.8%; 5.2%)]. In the 28-week SIRTURO arm at Week 132, 2/143 (1.4%) patients died; one of the two deaths was also related to TB. The overall mortality for patients treated with SIRTURO was 17/383 (4.4%).

Clinical Studies Experience in Pediatric Patients

The safety assessment of bedaquiline is based on the Week 24 analysis of the single-arm, open-label trial, TMC207-C211, in 15 pediatric patients. The trial was designed to enroll patients 12 to less than 18 years of age (only patients 14 to less than 18 years of age were enrolled) with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampin who received SIRTURO at the recommended dosage regimen in combination with a background regimen [see *Clinical Studies*].

The most common adverse drug reactions were arthralgia in 6/15 (40%) patients, nausea in 2/15 (13%) patients, and abdominal pain in 2/15 (13%) patients. Among the 15 patients, no deaths occurred during treatment with SIRTURO. Observed laboratory abnormalities were comparable to those in adults.

4.9 Overdose

There is no experience with the treatment of acute overdose with SIRTURO. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QTc interval) in case of deliberate or accidental overdose. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma.

5 Pharmacological Properties

Mechanism of Action

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

5.1 Pharmacodynamic Properties

Bedaquiline has activity against *M. tuberculosis*. The major metabolite, M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (3-fold to 6-fold lower) compared to the parent compound. However, M2 plasma concentrations are correlated with QTc prolongation.

Cardiac Electrophysiology

In Study 1, the largest mean increase in QTc during the 24 weeks of SIRTURO treatment was 16 ms compared to 6 ms with placebo treatment (at Week 18). After SIRTURO

treatment ended, the QTc gradually decreased, and the mean value was similar to that in the placebo group by study Week 60.

In Study 4, the mean change from baseline in QTc for the SIRTURO-containing arm was 22 ms (95 % CI: 19; 24) at Week 2 (i.e., the end of the 2-week SIRTURO loading period), and 8 ms (95 % CI: 2; 13) in the levofloxacin-containing control arm subgroup.

In Study 4, the mean QTc increased from baseline over the first 12 weeks for both SIRTURO and the non-SIRTURO containing control arm, when a plateau was reached. The largest mean QTc increase from baseline was 35 ms (95% CI: 32 to 38 ms) for the SIRTURO-containing arm and 28 ms (95% CI: 21 to 34 ms) for the levofloxacin-containing control arm subgroup [see *Special Warnings and Precautions for use (4.4.1) and Interaction with other medicinal products and other forms of interactions (4.5.3)*].

CLINICAL STUDIES

5.1.1 Adult Patients

Study 1 (NCT00449644, Stage 2) was a placebo-controlled, double-blind, randomized trial conducted in patients with newly diagnosed sputum smear-positive pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid. Patients were randomized to receive a combination of SIRTURO or placebo with five other antimycobacterial drugs (i.e., ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative) for a total duration of 18 to 24 months or at least 12 months after the first confirmed negative culture. Treatment was 24 weeks of treatment with SIRTURO 400 mg once daily for the first two weeks followed by 200 mg three times per week for 22 weeks or matching placebo for the same duration. Overall, 79 patients were randomized to the SIRTURO arm and 81 to the placebo arm. A final evaluation was conducted at Week 120.

Sixty-seven patients randomized to SIRTURO and 66 patients randomized to placebo had confirmed pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid, based on susceptibility tests (taken prior to randomization) or medical history if no susceptibility results were available, and were included in the efficacy analyses. Demographics were as follows: 64% of the study population was male, with a median age of 33 years, 38% were Black, 17% were Hispanic, 11% were White, 11% were Asian, and 24% were of another race; and 14% were HIV-positive (median CD4 cell count 446 cells/ μ L). Most patients had cavitation in one lung (62%); and 20% of patients had cavitation in both lungs.

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 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 at Week 24 and Week 120.

Table 4: Culture Conversion Status and Clinical Outcome at Week 24 and Week 120 in Study 1

Microbiologic Status	SIRTURO (24 weeks) + combination of other antimycobacterial drugs N=67	Placebo (24 weeks) + combination of other antimycobacterial drugs N=66	Difference [95% CI] p-value
Week 24			
Sputum Culture Conversion	78%	58%	20.0% [4.5%, 35.6%] 0.014
Treatment failure ^a	22%	42%	
Died	1%	0%	
Lack of conversion	21%	35%	
Discontinuation	0%	8%	
Week 120^b			
Sputum Culture Conversion	61%	44%	17.3% [0.5%, 34.0%] 0.046
Treatment failure ^a	39%	56%	
Died	12%	3%	
Lack of conversion/relapse	16%	35%	
Discontinuation	10%	18%	

^a A patient's reason for treatment failure was counted only in the first row for which a patient qualifies.

^b Patients received 24 weeks of SIRTURO or placebo for the first 24 weeks and received a combination of other antimycobacterial drugs for up to 96 weeks.

Study 2 (NCT00449644, Stage 1) was a smaller placebo-controlled study designed similarly to Study 1 except that SIRTURO or placebo was given for only eight weeks instead of 24 weeks. Patients were randomized to either SIRTURO and other drugs used to treat pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid (SIRTURO treatment group) (n=23) or placebo and other drugs used to treat 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 pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid based on patients' 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.

Study 3 (NCT00910871) was a Phase 2b, uncontrolled study to evaluate the safety, tolerability, and efficacy of SIRTURO as part of an individualized treatment regimen in 233 patients with sputum smear positive (within 6 months prior to screening) pulmonary TB due to *M. tuberculosis* resistant to at least rifampin and isoniazid, including patients with isolates resistant to second line injectables and/or fluoroquinolones. Patients received SIRTURO for 24 weeks in combination with antimycobacterial drugs. Upon completion of the 24 week treatment with SIRTURO, all patients continued to receive their background regimen in accordance with national TB program (NTP) treatment guidelines. A final evaluation was conducted at Week 120. Treatment responses to SIRTURO at week 120 were generally consistent with those from Study 1.

Study 4 (NCT02409290) was a Phase 3, open-label, multicenter, active-controlled, randomized trial to evaluate the efficacy and safety of SIRTURO, coadministered with other oral anti-TB drugs for 40 weeks in patients with sputum smear-positive pulmonary TB caused by *M. tuberculosis* that was resistant to at least rifampin. Patients in whom the *M. tuberculosis* strain was known to be resistant at screening to second-line injectable agents or fluoroquinolones were excluded from enrollment. When phenotypic susceptibility testing of the baseline isolates became available post-randomization, patients infected with *M. tuberculosis* resistant to either second-line injectable agents or fluoroquinolones were kept in the study, however, those with *M. tuberculosis* resistant to both second-line injectables and fluoroquinolones were discontinued from the study.

Patients were randomized to one of four treatment arms:

- Arm A (N=32), the locally used treatment in accordance with 2011 WHO treatment guidelines with a recommended 20-month duration
- Arm B (N=202), a 40-week treatment of moxifloxacin (N=140) or levofloxacin (N=62), clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)
- Arm C (N=211), a 40-week, all-oral treatment of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)
- Arm D (N=143), a 28-week treatment consisting of SIRTURO, levofloxacin, clofazimine, and pyrazinamide, supplemented by kanamycin injectable and a higher isoniazid dose for the first eight weeks (intensive phase)

SIRTURO was administered 400 mg once daily for the first two weeks and 200 mg three times a week for the following 38 weeks (in Arm C) or 26 weeks (in Arm D).

All patients were to be followed up until study completion at Week 132. During study conduct, enrollment in Arms A and D was stopped due to changes in the standard of care for TB treatment. Patients already randomized to these study arms were to complete their assigned treatment and follow-up.

The primary objective was to assess whether the proportion of patients with a favorable efficacy outcome in Arm C was noninferior to that in Arm B at Week 76.

The primary efficacy outcome measure was the proportion of patients with a favorable outcome at Week 76. A favorable outcome at Week 76 was defined as the last two consecutive cultures being negative, and with no unfavorable outcome. An unfavorable outcome at Week 76 was assessed as a composite endpoint, covering both clinical and microbiological aspects such as changes in TB treatment, all-cause mortality, at least one of the last two culture results positive, or no culture results within the Week 76 window. In case of treatment failure, recurrence or serious toxicity on the allocated treatment, salvage treatment that could include SIRTURO was provided, based on investigator judgment.

The modified intent-to-treat population (mITT) was the primary efficacy population and included all randomized patients with a positive sputum culture for *M. tuberculosis* that was resistant to at least rifampin and not resistant to both second-line injectables and fluoroquinolones, based on susceptibility results (taken prior to randomization). A total of 196 and 187 patients were included in the mITT population in Arm C and Arm B, respectively. Overall, in both treatment arms, 62% were male of median age 33 years, 47% were Asian, 34% were Black, 19% were White, and 14% were HIV-coinfected. Most patients had lung cavitation (74%), with multiple cavities in 63% and 47% of patients in Arm C and Arm B, respectively. The baseline drug resistance profile of *M. tuberculosis* for Arms C and B were as follows: 14% had resistance to rifampin while susceptible to isoniazid, 75% had resistance to rifampin and isoniazid, and 10% had resistance to rifampin, isoniazid, and either a second-line injectable or a fluoroquinolone.

For efficacy analyses beyond Week 76, data collection was stopped at the point when the last recruited patient was projected to reach Week 96. The long-term efficacy data therefore include data up to at least Week 96 for all patients, and up to Week 132 for 146/196 (74.5%) patients in Arm C and 145/187 (77.5%) patients in Arm B.

Table 5 shows results for favorable and unfavorable outcomes at Week 76 and Week 132 in Study 4.

Table 5: Clinical Outcome at Week 76 and Week 132 in the mITT Population in Study 4

	SIRTURO^a (N=196)	Active Control^b (N=187)
Favorable outcome at Week 76 n (%)	162 (82.7)	133 (71.1)
Difference ^c SIRTURO ^a vs Active Control ^b (95% CI)	11.0% (2.9%, 19.0%)	
Unfavorable outcome at Week 76 n (%)	34 (17.3)	54 (28.9)
Reasons for unfavorable outcome through Week 76 ^d		
Treatment modified or extended	16 (8.2)	43 (23.0)
No culture results within Week 76 window	12 (6.1)	7 (3.7)

Death through Week 76	5 (2.6)	2 (1.1)
At least one of last 2 cultures positive at Week 76	1 (0.5)	2 (1.1)
Favorable outcome at Week 132 n (%)^e	154 (78.6)	129 (69.0)
Difference ^c SIRTURO ^a vs Active Control ^c (95% CI)	9.0% (0.6%,17.5%)	

mITT = modified intent-to-treat

- ^a Arm C 40-week, all-oral regimen of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase).
- ^b Arm B 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high dose isoniazid and prothionamide in the first 16 weeks (intensive phase).
- ^c The adjusted difference in proportions was estimated using a stratified analysis of the risk difference from each stratum using Cochran Mantel-Haenszel weights. The analysis was stratified by randomization protocol and HIV and CD4 cell count status.
- ^d Patients were classified by the first event that made the patient unfavorable. Of the patients with an unfavorable outcome at Week 76 in the control arm, 29 patients had a treatment modification from their allocated treatment that included SIRTURO as part of a salvage regimen.
- ^e Week 132 outcome reflects efficacy follow up until the last patient reached Week 96.

5.1.2 Pediatric Patients (12 to less than 18 years of age)

The pediatric trial, TMC207-C211(NCT02354014), was designed as a single-arm, open-label, trial to evaluate the pharmacokinetics, safety and tolerability of SIRTURO in combination with a background regimen in patients 12 to less than 18 years of age with confirmed or probable pulmonary TB due to *M. tuberculosis* resistant to at least rifampin. Fifteen patients 14 to less than 18 years of age were enrolled in the study. The median age was 16 years, 80% were female, 53% were Black, 33% were White and 13% were Asian. No patient 12 to less than 14 years of age was enrolled in the study. SIRTURO was administered as 400 mg once daily for the first two weeks and 200 mg three times/week for the following 22 weeks.

In the subset of patients with culture positive pulmonary TB resistant to at least rifampin at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 75.0% (6/8 patients) at Week 24.

5.2 Pharmacokinetic Properties

Pharmacokinetics (PK) parameters

The pharmacokinetic properties of bedaquiline are summarized in Table 6 as mean (SD) in adult patients.

Table 6: Model-Derived Pharmacokinetic Parameters of Bedaquiline and M2 (mean [SD]) after Multiple Doses of SIRTURO at the Recommended Dosing Regimen

Pharmacokinetic Parameters	Bedaquiline
Absorption	

Food effect	High fat meal (22 grams of fat, 558 total Kcal) increased C_{max} and AUC by 2-fold. SIRTURO should be taken with food to enhance its oral bioavailability.
T_{max}	Around 5 hours after single oral dose administration of SIRTURO
C_{max} of bedaquiline	Week 2: 3060 (1124) ng/mL Week 24: 1838 (684) ng/mL Week 40: 1787 (666) ng/mL
C_{max} of M2	Week 2: 326 (135) ng/mL Week 24: 234 (85) ng/mL Week 40: 246 (103) ng/mL
Exposure	
AUC _{168h} of bedaquiline (AUC _{24h} for Week 2)	Week 2: 41510 (15064) ng.h/mL Week 24: 163924 (55710) (ng.h/mL) Week 40: 168376 (74476) ng.h/mL
AUC _{168h} of M2 (AUC _{24h} for Week 2)	Week 2: 7267 (3029) ng.h/mL Week 24: 37255 (13998) ng.h/mL Week 40: 39540 (17220) ng.h/mL
Distribution	
Percent bound to human plasma protein	greater than 99.9%.
apparent central volume of distribution	approximately 117 Liters.
Proportionality	C_{max} and AUC increased proportionally up 700 mg (1.75 times the 400 mg loading dose).
Elimination	After reaching C_{max} , bedaquiline concentrations decline tri-exponentially.
Apparent clearance of bedaquiline	2.62 L/h
Apparent clearance of M2	4.95 L/h

Terminal half-life	~ 5.5 months for both bedaquiline and <i>N</i> monodesmethyl metabolite (M2)
Metabolism	Metabolized to the M2 by CYP3A4; Relative exposure M2 versus bedaquiline: 23%~31%
Excretion	
Major route of excretion	Fecal excretion is the major route of elimination
%Excreted unchanged in urine	less than or equal to 0.001% of the dose in clinical studies

SD=Standard Deviation

Specific Populations

Hepatic Impairment: After single-dose administration of 400 mg SIRTURO to 8 adult patients with moderate hepatic impairment (Child-Pugh B), mean exposure to bedaquiline and M2 (AUC_{672h}) was approximately 20% lower compared to healthy adults. SIRTURO has not been studied in patients with severe hepatic impairment. [see *Special Warnings and Precautions for use (4.4.4) and Posology and method of administration (4.2.7)*].

Renal Impairment: SIRTURO has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged bedaquiline is not substantial (less than or equal to 0.001%).

In a population pharmacokinetic analysis of adult 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. However, in patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis 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 [see *Posology and method of administration (4.2.8)*].

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

Race/Ethnicity: In a population pharmacokinetic analysis of adult 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 bedaquiline exposure in Black patients was not associated with lower efficacy in clinical trials.

HIV Coinfection: Bedaquiline exposure in patients coinfecting with HIV was similar to that

of patients not infected with HIV.

Geriatric Population: There are limited data on the use of SIRTURO in TB patients 65 years of age and older.

In a population pharmacokinetic analysis of adult TB patients treated with SIRTURO, age was not found to influence the pharmacokinetics of bedaquiline. In five patients 65 to 69 years of age, the systemic bedaquiline exposure was similar to that in other adults.

Pediatric Population: The pharmacokinetic parameters of bedaquiline in 15 pediatric patients 14 to less than 18 years of age who received the same adult dosage regimen of SIRTURO (400 mg once daily for the first two weeks and 200 mg three times/week for the following 22 weeks) in combination with a background regimen were comparable to those in adults; see Table 7 below for a summary of the pharmacokinetic parameters. There was no impact of body weight on bedaquiline pharmacokinetics in pediatric patients 14 to less than 18 years of age (38 to 75 kg).

Table 7: Pharmacokinetic Parameters of Bedaquiline Following Repeat Dose Administration of SIRTURO to Pediatric Patients 14 to less than 18 years of age at Week 12 Administered with Food (N=15)

Pharmacokinetic Parameter	Bedaquiline Mean (SD)
AUC_{24h} (ng•h/mL)	26,300 (10,300)
C_{max} (ng/mL)	1,800 (736)
T_{max} (h)*	4 (2-8)
C_{min} (ng/mL)	544 (263)
SD=Standard Deviation	
* Median (range)	

The pharmacokinetics of SIRTURO in pediatric patients less than 14 years of age or weighing less than 38 kg have not been evaluated.

Drug Interactions Studies

In vitro, bedaquiline did 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.

Bedaquiline is an *in vitro* substrate of CYP3A4, and because of this, the following clinical drug interaction studies were performed.

Clinical Studies

Ketoconazole: Coadministration of multiple-dose bedaquiline (400 mg once daily for 14 days) and multiple-dose ketoconazole (once daily 400 mg for 4 days) in healthy adult 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 [see *Interaction with other*

medicinal products and other forms of interactions (4.5.1) and (4.5.3)].

Clarithromycin: Coadministration of a single 100 mg dose of SIRTURO with clarithromycin at steady-state in healthy adults increased the mean [90% CI] bedaquiline exposure AUC_{240h} by 14% [9%;19%].

Clofazimine: In Study 3, long-term coadministration of clofazimine and SIRTURO, as part of a combination therapy for up to 24 weeks, did not affect bedaquiline exposure.

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 adult subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)] [*see Interaction with other medicinal products and other forms of interactions (4.5.1)*]

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 adult subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide [*see Interaction with other medicinal products and other forms of interactions (4.5.2)*]

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

Lopinavir/ritonavir: In a drug interaction study in healthy adults of single-dose bedaquiline (400 mg) and multiple-dose lopinavir (400 mg)/ritonavir (100 mg) 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 In Study 4, coadministration of SIRTURO with lopinavir/ritonavir in patients coinfecting with HIV increased bedaquiline exposure, with an estimated 68% [90% CI (29%; 117%)] increase in mean AUC_{168h} at Week 24 and 72% [90% CI (32%; 123%)] at Week 40, in HIV-positive Black patients treated with lopinavir/ritonavir (N=16) compared to HIV-positive and -negative Black patients without lopinavir/ritonavir (N=67) treatment [*see Interaction with other medicinal products and other forms of interactions (4.5.1)*]

Nevirapine: Coadministration of multiple-dose nevirapine 200 mg twice daily for 4 weeks in HIV-infected adult patients with a single 400 mg dose of bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline. In Study 4, coadministration of nevirapine and SIRTURO as part of combination therapy for up to 40 weeks in patients coinfecting with HIV, resulted in a 29% [90% CI (0; 50%)] decrease in bedaquiline exposure (AUC_{168h}).

Efavirenz: Co-administration of a single dose of bedaquiline 400 mg and efavirenz 600 mg daily for 27 days to healthy adult volunteers resulted in approximately a 20% decrease in the AUC_{inf} of bedaquiline; the C_{max} of bedaquiline was not altered. The AUC and C_{max} of

the primary metabolite of bedaquiline (M2) were increased by 70% and 80%, respectively. The effect of efavirenz on the pharmacokinetics of bedaquiline and M2 following steady-state administration of bedaquiline has not been evaluated [see *Interaction with other medicinal products and other forms of interactions (4.5.3)*]

Microbiology

Mechanism of Action

SIRTURO is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *M. tuberculosis*.

Resistance

A potential for development of resistance to bedaquiline in *M. tuberculosis* exists. Modification of the *atpE* target gene, and/or upregulation of the MmpS5-MmpL5 efflux pump (*Rv0678* mutations) have been associated with increased bedaquiline MIC values in isolates of *M. tuberculosis*. Target-based mutations generated in preclinical studies lead to 8- to 133-fold increases in bedaquiline MIC, resulting in MICs ranging from 0.25 to 4 micrograms per mL. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to 2- to 8-fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0.25 to 0.5 micrograms per mL.

M. tuberculosis isolates that had developed at least a 4-fold increase in bedaquiline MIC were associated with mutations in *Rv0678* gene that lead to upregulation of the MmpS5-MmpL5 efflux pump. Isolates with these efflux-based mutations are less susceptible to clofazimine. Isolates that are phenotypically resistant to bedaquiline should be tested for cross-resistance to clofazimine, if clofazimine is being considered as part of the treatment regimen. In Studies 2, 3 and 4 there was no clear relationship between the presence of *Rv0678* mutations at baseline and treatment outcome.

Antimicrobial Activity

SIRTURO has been shown to be active *in vitro* and in clinical infections against most isolates of *M. tuberculosis* [see *Therapeutic Indication (4.1)* and *Clinical Studies*].

Susceptibility Testing

MICs for baseline *M. tuberculosis* isolates from patients in Studies 1 and 3 and their sputum culture conversion rates at Week 24 and from patients in the 40-week SIRTURO arm of Study 4 at Week 76 are shown in Table 8 below. Based on the available data, there was no relationship between poor microbiologic outcomes and baseline bedaquiline MIC.

Table 8: Culture Conversion Rates in SIRTURO Treatment Groups at Week 24 (Study 1 and 3) and at Week 76 (Study 4), by Baseline Bedaquiline MIC (mITT population)^a

Baseline Bedaquiline MIC (micrograms/mL)	SIRTURO Treatment Group 24-Week Culture Conversion Rate (Study 1 and Study 3) n/N (%)	SIRTURO Treatment Group 76-Week Culture Conversion Rate (Study 4, 40-Week Arm) ^b n/N (%)
≤ 0.008	2/2 (100)	5/5 (100)
0.015	13/15 (86.7)	26/26 (100)
0.03	36/46 (78.3)	67/69 (97.1)
0.06	82/107 (76.6)	51/51 (100)
0.12	36/42 (85.7)	20/20 (100)
0.25	3/4 (75.0)	2/2 (100)
0.5	5/6 (83.3)	0
≥ 1	0/1 (0)	0

N=number of patients with data per baseline BDQ MIC category; n=number of patients with culture conversion; MIC=minimum inhibitory concentration

^a 7H11 agar. Patients who prematurely discontinued were categorized as culture converted (or not) based on the available data. All available data were utilized regardless of changes in treatment.

^b In addition, at Week 76 in the 40-week SIRTURO arm, there were 6 patients for whom no baseline MIC data were available. All 6 patients culture converted.

Nineteen patients in the efficacy population of Study 3 had bedaquiline susceptibility testing results of paired (baseline and post-baseline, all of which were at Week 24 or later) genotypically identical *M. tuberculosis* isolates. Twelve of the 19 had a post-baseline ≥4-fold increase in bedaquiline MIC. Whole genome sequencing of nine of these 12 post-baseline isolates was done and no mutations were found in the ATP synthase operon. All nine were found to have a mutation in *Rv0678*. Eleven of the twelve (11/12) increases in bedaquiline MIC were seen in patients with isolates that also demonstrated increase MICs to fluoroquinolones and/or second-line injectables.

Based on available data, response rate (culture conversion at Week 120 endpoint) was similar in patients with ≥4-fold increases in bedaquiline MIC (5/12) and patients with < 4-fold increases (3/7).

In the 40-week SIRTURO arm of Study 4, paired isolates (baseline and postbaseline, genotypically identical) susceptibility testing (MIC) results were available for 30 of 196 patients in the mITT population. At Week 132, three of five patients with a ≥4-fold increase in bedaquiline MIC and 25 of 25 patients with <4-fold increases had culture converted. Similarly, in the 28-week arm of Study 4, for 25 of 134 patients in the mITT population with paired isolates, two of four patients, with a ≥4-fold increase in bedaquiline MIC and 20 of 21 patients with <4-fold increases had culture converted. Based on the limited data, there was no clear relationship between bedaquiline MIC and microbiological outcomes.

5.3 Preclinical Safety Data

5.3.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Bedaquiline was not carcinogenic in rats up to the maximum tolerated dose of 10 mg/kg/day. Exposures at this dose in rats (AUCs) were within 1-fold to 2-fold of those observed in adult patients in the clinical trials.

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 did not affect fertility when evaluated in male and female rats at approximately twice the clinical exposure based on AUC comparisons. There was no effect of maternal treatment on sexual maturation, mating performance or fertility in F1 generation exposed to bedaquiline *in utero* at approximately twice the human exposure.

5.3.2 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.

6 Pharmaceutical Particulars

6.1 List of excipients

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).

6.2 Incompatibilities

no information in USPI

6.3 Shelf life

See expiry date on the outer pack

6.4 Special precautions for storage

Dispense in original container. Store tablets dispensed outside the original container in a tight light-resistant container with an expiration date not to exceed 3 months.

Do not store above 30°C. See expiry date on the outer pack.

Protect from light. Keep the container tightly closed.

Keep out of reach of children.

6.5 Nature and contents of container

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.

7 Marketing Authorization Holder

Manufactured by

Recipharm Pharmservices Pvt. Ltd.

Bangalore, India

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com

8 Marketing Authorization Numbers

1C 5/60 (N)

9 Date of authorization

24 August 2017

10 Date of SMP Released Approval

16 January 2023

11 Date of revision of the text

USPI version Jun 2024

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Adverse Reactions

Advise patients that the following serious side effects can occur with SIRTURO: heart rhythm abnormalities, death and/or hepatitis. In addition, advise patients about other potential side effects: nausea, vomiting, joint pain, increased transaminases, dizziness, headache, myalgia, diarrhea, increased blood amylase, hemoptysis, chest pain, anorexia,

rash, and/or abdominal pain. Additional testing may be needed to monitor or reduce the likelihood of adverse effects.

Compliance with Treatment

Advise patients to take SIRTURO in combination with other antimycobacterial drugs as prescribed. Emphasize compliance with the full course of therapy. Advise patients that 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 antimycobacterial drugs in the future.

If a dose is missed during the first 2 weeks of treatment, advise patients not to make up the missed dose but to continue the usual dosing schedule. From Week 3 onwards, if a dose is missed, advise patients to take the missed dose as soon as possible, and then resume the 3 times a week regimen. Ensure that the total dose of SIRTURO during a 7-day period does not exceed the recommended weekly dose (with at least 24 hours between each intake).

Administration Instructions

Advise patients to take SIRTURO with food.

Use with Alcohol and other Medications

Instruct patients to abstain from alcohol, hepatotoxic medications or herbal products.

Advise patients to discuss with their physician the other medications they are taking and other medical conditions before starting treatment with SIRTURO.

Lactation

Advise patients not to breastfeed during treatment with SIRTURO and for 27.5 months after the last dose unless infant formula is not available. If an infant is exposed to bedaquiline through breast milk, advise caregivers to monitor the infant for signs of bedaquiline-related adverse reactions, such as hepatotoxicity (yellowing of the eyes and changes in the color of the urine or stool) [*see Undesirable effects (4.8) and Pregnancy and lactation (4.6.2)*].