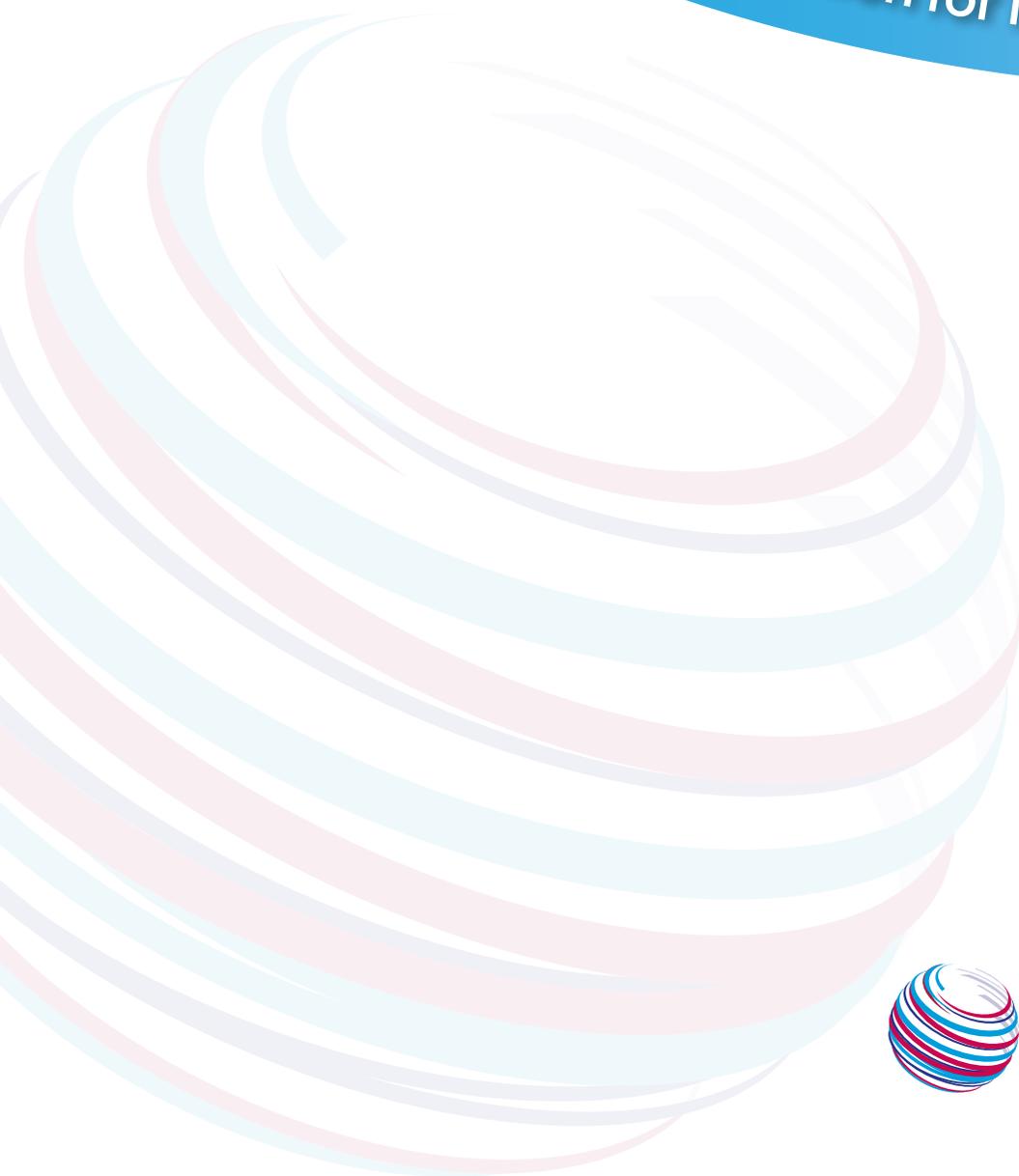


SIRTURO[®] product information for healthcare providers



Sirturo[®]
bedaquiline tablets
20mg/100mg

WARNINGS: INCREASED MORTALITY AND QT PROLONGATION

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 in adults. Only use SIRTURO® in patients 5 years of age and older when an effective treatment regimen cannot otherwise be provided.

QT PROLONGATION

- QT prolongation can occur with SIRTURO®. Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs. Discontinue SIRTURO® if significant ventricular arrhythmia or if QTcF interval prolongation of greater than 500 ms develops.

Indications and Usage

SIRTURO® is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (5 years and older and weighing at least 15 kg) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO® for use when an effective treatment regimen cannot otherwise be provided.

This indication is approved under accelerated approval based on time to sputum culture conversion. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of Use:

Do not use SIRTURO® for the treatment of:

- Latent infection due to *Mycobacterium tuberculosis*
- Drug-sensitive tuberculosis
- Extra-pulmonary tuberculosis
- Infections caused by non-tuberculous mycobacteria

The safety and efficacy of SIRTURO® in the treatment of HIV-infected patients with MDR-TB have not been established as clinical data are limited

Dosage and Administration

Important Administration Instructions

- Administer SIRTURO® by directly observed therapy (DOT).
- Only use SIRTURO® 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, SIRTURO® treatment may be initiated in combination with at least 4 other drugs to which the patient's MDR-TB isolate is likely to be susceptible. Refer to the prescribing information of the drugs used in combination with SIRTURO® for further information.
- SIRTURO® (20-mg and 100-mg) must be taken with food.
- SIRTURO® 20-mg are functionally scored tablets which can be split at the scored lines into 2 equal halves of 10-mg each to provide doses less than 20-mg
- As an alternative method of administration, SIRTURO® 20-mg tablets can be dispersed in water and administered, or

dispersed in water and further mixed with a beverage or soft food, or crushed and mixed with soft food, or administered through a nasogastric tube.

- Emphasize the need for compliance with the full course of therapy.

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
- ECG
- Serum potassium, calcium, and magnesium concentrations
- Liver enzymes

Recommended Dosage in Combination Therapy

Adult Patients: Recommended Dosage of SIRTURO®

Weeks 1 and 2	Weeks 3 to 24 ^a
400-mg (4 of the 100-mg tablets OR 20 of the 20-mg tablets) orally once daily	200-mg (2 of the 100-mg tablets OR 10 of the 20-mg tablets) orally 3 times per week
a=At least 48 hours between doses	

The total duration of treatment with SIRTURO® in adults is 24 weeks. Administer SIRTURO® tablets with food.

Pediatric Patients:

Recommended Dosage of SIRTURO® in Pediatric Patients (5 years and older and weighing at least 15 kg)

Body Weight	Dosage Recommendation	
	Weeks 1 and 2	Weeks 3 to 24 ^a
15 kg to less than 30 kg	200-mg (2 of the 100-mg tablets OR 10 of the 20-mg tablets) orally once daily	100-mg (1 of the 100-mg tablets OR 5 of the 20-mg tablets) orally 3 times per week
Greater than or equal to 30 kg	400-mg (4 of the 100-mg tablets OR 20 of the 20-mg tablets) orally once daily	200-mg (2 of the 100-mg tablets OR 10 of the 20-mg tablets) orally 3 times per week
a=At least 48 hours between doses		

The total duration of treatment with SIRTURO® in pediatric patients is 24 weeks. Administer SIRTURO® tablets with food.

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 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)

Method of Administration

There is one method of administration of SIRTURO® 100-mg tablet and 4 different methods of administration of SIRTURO® 20-mg tablet as follows:

- For SIRTURO® 100-mg tablet, administer the tablet whole with water. Take with food.
- For SIRTURO® 20-mg tablet, the 4 different methods of administration are outlined below. Each administration method requires SIRTURO® to be taken with food.

Methods of Administration of SIRTURO® 20-mg Tablet

Administration of 20-mg Tablets to Patients Who Can Swallow Intact Tablets:

Swallow Intact Tablets:

Administer SIRTURO® 20-mg tablet whole or divided in half along the functional score line into 2 equal halves of 10-mg each. Administer SIRTURO® 20-mg tablet with water. Take with food.

Administration of 20-mg Tablets to Patients Who Cannot Swallow Intact Tablets:

Swallow Intact Tablets:

Dispersed in Water and Administered With Beverage or Soft Food

For patients who have difficulty swallowing intact tablets, SIRTURO® 20-mg tablet can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage (e.g., water, milk products, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yogurt, apple sauce, mashed banana or porridge) as follows:

- Disperse tablets in water (maximum of 5 tablets in 5 mL of water) in a drinking cup.
- Mix the contents of the cup well until the tablets are completely dispersed and then orally administer the contents of the cup immediately with food. To aid with administration, the dispersed mixture in water can be further mixed with at least 5 mL of beverage or 1 teaspoonful of soft food and then orally administer the contents of the cup immediately.
- If the total dose requires more than 5 tablets, repeat the above preparation steps with the appropriate number of additional tablets until the desired dose is reached.
- Ensure no tablet residue is left in the cup, rinse with beverage or add more soft food and orally administer the contents of the cup immediately.

Crushed and Mixed with Soft Food

SIRTURO® 20-mg tablet can be **crushed and mixed with soft food** (e.g., yogurt, apple sauce, mashed banana or porridge) immediately prior to use and administered orally. Ensure no tablet residue is left in container, add more soft food and administer the contents immediately.

Administration Through a Nasogastric Tube

SIRTURO® 20-mg tablet can be administered through **a nasogastric tube** (8 French or greater) as follows

- Disperse 5 tablets or less in 50 mL of non-carbonated water and mix well. Mixture should be white to almost white with visible particles expected.
- Administer through the nasogastric tube immediately.
- Repeat with additional tablets until desired dose is reached.
- Rinse and flush with 25 mL of additional water to ensure no tablet residue is left in materials used for preparation or the nasogastric tube.

Warnings and Precautions

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 in adults (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. Only use SIRTURO® in patients 5 years of age and older when an effective treatment regimen cannot otherwise be provided.

QT Prolongation

SIRTURO® prolongs the QT interval. Obtain an ECG before initiation of treatment, and at least 2, 12, and 24 weeks after starting treatment with SIRTURO®. Obtain serum potassium, calcium, and magnesium at baseline and correct if abnormal. Monitor electrolytes if QT prolongation is detected.

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

The following may increase the risk for QT prolongation when patients are receiving SIRTURO®:

- 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 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

If necessary, SIRTURO® treatment initiation could be considered in these patients after a favorable benefit risk assessment and with frequent ECG monitoring.

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

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

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

Risk of Development of Resistance to Bedaquiline

A potential for development of resistance to bedaquiline in *Mycobacterium tuberculosis* exists. Bedaquiline must only be used in an appropriate combination regimen for the treatment of pulmonary MDR-TB to reduce the risk of development of resistance to bedaquiline.

Hepatotoxicity

In clinical trials, more hepatic-related adverse reactions were reported in adults with the use of SIRTURO® plus other drugs used to treat tuberculosis compared to other drugs used to treat tuberculosis 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 5 years of age and older.

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:

- Aminotransferase elevations are accompanied by total bilirubin elevation greater than 2 times the upper limit of normal
- Aminotransferase elevations are greater than 8 times the upper limit of normal
- Aminotransferase elevations are greater than 5 times the upper limit of normal and persist beyond 2 weeks

Drug Interactions

CYP3A4 Inducers/Inhibitors

SIRTURO® is metabolized by CYP3A4 and its systemic exposure and therapeutic effect may therefore be reduced during co-administration with inducers of CYP3A4. Avoid co-administration of strong CYP3A4 inducers, such as rifamycins (i.e., rifampin, rifapentine and rifabutin), or moderate CYP3A4 inducers, such as efavirenz, during treatment with SIRTURO®.

Co-administration of SIRTURO® with strong CYP3A4 inhibitors may increase the systemic exposure to SIRTURO®, which could potentially increase the risk of adverse reactions. Therefore, avoid the use of strong CYP3A4 inhibitors for more than 14 consecutive days while on SIRTURO®, unless the benefit of treatment with the drug combination outweighs the risk. Appropriate clinical monitoring for SIRTURO®-related adverse reactions is recommended.

Adverse Reactions

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

- Increased Mortality [see Warnings and Precautions]
- QT Prolongation [see Warnings and Precautions]
- Hepatotoxicity [see Warnings and Precautions]
- Drug Interactions [see Warnings and Precautions]

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.

Clinical Studies Experience in Adults

Adverse reactions for SIRTURO® were identified from the pooled safety data from 335 SIRTURO®-exposed patients who received 8 weeks (Study 2) and 24 weeks (Studies 1 and 3) at the proposed dose. Studies 1 and 2 were randomized, double-blind, placebo-controlled trials 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 was an open-label, noncomparative study with SIRTURO® administered as part of an individualized pulmonary MDR-TB treatment regimen in previously treated patients.

In Study 1, 35% 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 6 (7.4%) placebo-treated patients discontinued Study 1 because of an adverse reaction (Table 1).

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

In both Studies 1 and 2, aminotransferase 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.

Increased Mortality

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%] vs 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 tuberculosis-related. One death occurred during the 24-week SIRTURO® treatment period. The median time to death for the remaining 8 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 tuberculosis, HIV status, and severity of disease was observed.

In the open-label Study 3, 6.9% (16/233) patients died. The most common cause of death as reported by the investigator was TB (9 patients). All but one patient who died of TB had not converted or had relapsed. The causes of death in the remaining patients varied.

Clinical Studies Experience in Pediatric Patients

The safety assessment of bedaquiline is based on the Week 24 analysis from 30 pediatric patients in an ongoing, single-arm, open-label, multi-cohort trial (Study 4).

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

The first cohort was designed to enroll patients 12 years to less than 18 years of age (15 patients 14 years to less than 18 years of age were enrolled) with confirmed or probable pulmonary MDR-TB infection who received SIRTURO® (400-mg once daily for the first 2 weeks and 200-mg 3 times/week for the following 22 weeks) in combination with a background regimen.

The most common adverse 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.

Pediatric Patients (5 years to less than 12 years of age)

The second cohort was designed to enroll patients 5 years to less than 12 years of age (15 patients aged 5 years to less than 11 years of age were enrolled) with confirmed or probable pulmonary MDR-TB infection who received SIRTURO® (200-mg once daily for the first 2 weeks and 100-mg 3 times/week for the following 22 weeks) in combination with a background regimen.

The most common adverse reactions were related to elevations in liver enzymes (5/15, 33%), and led to discontinuation of SIRTURO® in three patients. Elevations in liver enzymes were reversible upon discontinuation of SIRTURO® and some of the background regimen drugs. Among these 15 pediatric patients, no deaths occurred during treatment with SIRTURO®.

Drug Interactions

CYP3A4 Inducers/Inhibitors

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

CYP3A4 Inducers

Due to the possibility of a reduction of the therapeutic effect of SIRTURO® because of the decrease in systemic exposure, co-administration of strong CYP3A4 inducers, such as rifamycins (i.e., rifampin, rifapentine and rifabutin), or moderate CYP3A4 inducers should be avoided during treatment with SIRTURO®.

CYP3A4 inhibitors

Due to the potential risk of adverse reactions to SIRTURO® because of the increase in systemic exposure, prolonged co-administration of SIRTURO® and strong CYP3A4 inhibitors, such as ketoconazole or itraconazole, for more than 14 consecutive days should be avoided unless the benefit outweighs the risk. Appropriate clinical monitoring for SIRTURO®-related adverse reactions is recommended.

Other Antimicrobial Medications

No dose adjustment of isoniazid or pyrazinamide is required during co-administration with SIRTURO®.

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

Antiretroviral Medications

Lopinavir/ritonavir

Although clinical data in HIV/MDR-TB co-infected patients on the combined use of lopinavir (400-mg)/ritonavir (100-mg) with SIRTURO® are not available, use SIRTURO® with caution when co-administered with lopinavir/ritonavir and only if the benefit outweighs the risk.

Nevirapine

No dosage adjustment of SIRTURO® is required when co-administered with nevirapine.

Efavirenz

Concomitant administration of SIRTURO® and efavirenz, or other moderate CYP3A inducers, should be avoided.

QT Interval Prolonging Drugs

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

In Study 3, mean increases in QTc were larger in the 17 adult patients who were taking clofazimine with SIRTURO® at Week 24 (mean change from reference of 31.9 ms) than in patients who were not taking clofazimine with SIRTURO® at Week 24 (mean change from baseline of 12.3 ms). Monitor ECGs if SIRTURO® is co-administered to patients receiving other drugs that prolong the QTc interval, and discontinue SIRTURO® if evidence of serious ventricular arrhythmia or QTcF interval greater than 500 ms.

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

Adverse Reactions	SIRTURO® Treatment Group N=79 n (%)	Placebo Treatment 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.



Please see Important Safety Information, including Boxed Warnings, on pages 2-6.

Use in Specific Populations

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 tuberculosis during pregnancy.

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. 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 tuberculosis 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 6-17, 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 6-19, 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.

Lactation

Risk Summary

There is no information regarding the presence of bedaquiline in human milk. Minimal data are available on the effects of the drug on breastfed infants. No data are available on the effects of the drug on milk production. Bedaquiline is concentrated in the milk of rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SIRTURO® and any potential adverse effects on the breastfed infant from SIRTURO® or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to bedaquiline through breast milk for signs of bedaquiline-related adverse reactions, such as hepatotoxicity.

Data

Bedaquiline concentrations in rat milk were 6-fold to 12-fold higher than the maximum concentration observed in maternal plasma at exposures 1 time to 2 times the clinical exposure (based on AUC comparisons). Pups from these dams were exposed to bedaquiline via milk during the lactation period and showed reduced body weights compared to control animals.

Pediatric Use

The safety and effectiveness of SIRTURO® have been established in pediatric patients 5 years and older weighing at least 15 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, multi-cohort trial that enrolled 30 pediatric patients 5 years to less than 18 years of age with confirmed or probable MDR-TB infection who were to be treated with SIRTURO® for 24 weeks in combination with a background regimen.

The safety, effectiveness and dosage of SIRTURO® in pediatric patients less than 5 years of age and/or weighing less than 15 kg have not been established.

Geriatric Use

Because of limited data, differences in outcomes or specific risks with SIRTURO® cannot be ruled out for patients 65 years of age and older.

Hepatic Impairment

The pharmacokinetics of SIRTURO® were assessed after single dose administration to adult patients with moderate hepatic impairment (Child Pugh B). 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.

Renal Impairment

SIRTURO® has mainly been studied in adult patients with normal renal function. Renal excretion of unchanged SIRTURO® 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. 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.

Clinical Studies

Adult Patients

A placebo-controlled, double-blind, randomized trial (**Study 1**) was conducted in patients with newly diagnosed sputum smear-positive MDR pulmonary *M. tuberculosis*. All patients received a combination of 5 other antimycobacterial drugs used to treat MDR-TB (i.e., ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative) for a total duration of 18-24 months or at least 12 months after the first confirmed negative culture. In addition to this regimen, patients were randomized to receive 24 weeks of treatment with SIRTURO® 400-mg once daily for the first 2 weeks followed by 200-mg 3 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 MDR-TB, 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:

Table 2: Culture Conversion Status in Patients With MDR-TB 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*	22%	42%	
Died	1%	0%	
Lack of conversion	21%	35%	
Discontinuation	0%	8%	
Week 120[†]			
Sputum Culture Conversion	61%	44%	17.3% [0.5%, 34.0%] 0.046
Treatment failure*	39%	56%	
Died	12%	3%	
Lack of conversion/ relapse	16%	35%	
Discontinuation	10%	18%	

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

[†]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.

63% of the study population was male, with a median age of 34 years, 35% were Black, and 15% were HIV-positive (median CD4 cell count 468 cells/μL). Most patients had cavitation in one lung (62%) and 18% 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 2 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 2 shows the proportion of patients with sputum culture conversion at Week 24 and Week 120.

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 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 was a Phase 2b, uncontrolled study to evaluate the safety, tolerability, and efficacy of SIRTURO® as part of an individualized MDR-TB treatment regimen in 233 patients with sputum smear positive (within 6 months prior to screening) pulmonary MDR-TB. Patients received SIRTURO® for 24 weeks in combination with antibacterial 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.



Please see Important Safety Information, including Boxed Warnings, on pages 2-6.

Pediatric Patients

The pediatric trial (Study 4, NCT02354014) was designed as a single-arm, open-label, multi-cohort trial to evaluate the pharmacokinetics, safety and tolerability of SIRTURO® in combination with a background regimen in patients 5 to less than 18 years of age with confirmed or probable pulmonary MDR-TB infection.

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

Fifteen patients ages 14 years to less than 18 years of age were enrolled in the first cohort. The median age was 16 years, 80% were female, 53% were Black, 33% were White and 13% were Asian. No patient 12 years to less than 14 years of age was enrolled in this cohort. SIRTURO® was administered as 400-mg once daily for the first 2 weeks and 200-mg 3 times/week for the following 22 weeks using the 100-mg tablet.

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

Pediatric Patients (5 years to less than 12 years of age)

Fifteen patients ages 5 years to 10 years of age were enrolled in the second cohort. The median age was 7 years, 60% were female, 60% were Black, 33% were White and 7% were Asian. No patient older than 10 years to less than 12 years of age was enrolled in this cohort. The body weight range was 14 kg to 36 kg; only 1 patient weighing 14 kg was enrolled. SIRTURO® was administered as 200-mg once daily for the first 2 weeks and 100-mg 3 times/week for the following 22 weeks using the 20-mg tablet.

In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3 patients) at Week 24.

Please read accompanying full Prescribing Information, including Boxed Warnings and Medication Guide, for more details.



For additional information, please visit www.SIRTURO.com.

Please read full Product Information, including Boxed WARNINGS and Medication Guide on www.SIRTURO.com

Janssen Therapeutics, Division of Janssen Products, LP

