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.

Indications and Usage

SIRTURO® is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adult and pediatric patients (12 or less than 18 years of age and weighing at least 30 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 of this indication is dependent upon confirmation of clinical benefit in confirmatory trials.

Limitations of Use:

- 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 12 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.

Dosage and Administration

**Important Administration Instructions**

- Administer SIRTURO® by directly observed therapy (DOT).
- Use SIRTURO® only in combination with other antimycobacterial drugs.
- Emphasize the need for compliance with 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
- ECC
- Serum potassium, calcium, and magnesium concentrations
- Liver enzymes

**Recommended Dosage in Combination Therapy**

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.

The recommended dosage of SIRTURO® in patients 12 years of age and older is 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally 3 times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks).

The SIRTURO® tablet should be swallowed whole with water and taken with food.

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.

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 12 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 florafloquinolones and macrolide antibacterial drugs and the antimycobacterials clofazimine and rifabutin.
- A history of congenital long QT syndrome
- A history of or ongoing bradyarrhythmias
- A history of or ongoing hypothyroidism
- 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.

**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®. If hepatitis is suspected, discontinue other hepatotoxic medications if evidence of new or worsening liver dysfunction occurs.

**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 14 to less than 18 years of age. 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.

If syncope occurs, obtain an ECG to detect QT prolongation. 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.
Indications and Usage
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 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 the lower limits of normal

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).
- Use SIRTURO® only in combination with other antimycobacterial drugs
- Emphasize the need for compliance with 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

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.

The recommended dosage of SIRTURO® in patients 12 years of age and older is 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally 3 times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks).

The SIRTURO® tablet should be swallowed whole with water and taken with food.

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.

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.

Only use SIRTURO® in patients 12 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 or if QTc interval prolongation of greater than 500 ms develops.

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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.

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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.

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.

Only use SIRTURO® in patients 12 years of age and older when an effective treatment regimen cannot otherwise be provided.

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Recommended Dosage in Combination Therapy

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.

The recommended dosage of SIRTURO® in patients 12 years of age and older is 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally 3 times per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks).

SIRTURO® tablets should be swallowed whole with water and taken with food.

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.
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.

Use SIRTURO® only in combination with other antitubercular drugs [see Dosage and Administration]. Refer to the prescribing information of the drugs used in combination with SIRTURO® for their respective adverse reactions.

Clinical Studies Experience in Adults

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

In both Studies 1 and 2, an amotransferase-elevation of at least 3 times the upper limit of normal developed more frequently in the SIRTURO® treatment group (7/72 [10.8%] vs 6/70 [8.6%]) than in the placebo treatment group. In Study 3, 22/320 (7.0%) patients had alanine aminotransferase 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 (7/72 [10.1%] vs 2/81 [2.5%], p-value = 0.03, an exact 95% confidence interval was 1.1% to 18.2%). Five of the 9 SIRTURO® deaths were tuberculosis-related. An additional 8 patients died for reasons other than MDR-TB: 1 of pill non-adherence, 1 of a helper T-cell deficiency, 2 of unknown reasons, 2 from other causes, and 2 from unknown causes.

In Study 2, 7/177 (3.9%) patients in the SIRTURO® group and 6/175 (3.4%) patients in the placebo group died. The causes of death were primarily from disease progression in both groups. The 1 SIRTURO®-treated patient who died from pill non-adherence had died of TB at 10 months. In Study 3, 18/230 (7.8%) patients died. The most common cause of death as reported by the investigator and 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

In 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 (but only 14 to less than 18 years old patients were enrolled) with confirmed or probable pulmonary MDR-TB infection who received SIRTURO® at the recommended dosage regimen, in combination with a background regimen.

The most common adverse drug reactions were arthralgia in 6/75 (9.3%) patients, nausea in 2/75 (3%) patients and abdominal pain in 2/75 (2.6%) patients. Among the 15 patients, no deaths occurred during treatment with SIRTURO®. Observed laboratory abnormalities were comparable to those in adults.

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 potential risk of adverse reactions, the co-administration of SIRTURO® with drugs that are strong inducers of CYP3A4 is not recommended. These drugs include, but are not limited to, rifampin, rifabutin, rifapentine, nelfinavir, and lopinavir/ritonavir.

**CYP3A4 Inhibitors**

Due to the potential risk of adverse reactions, the co-administration of SIRTURO® with drugs that are strong inhibitors of CYP3A4 is not recommended. These drugs include, but are not limited to, ketoconazole, itraconazole, and quinolones.

**Other Antimicrobial Medications**

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

**Nevirapine**

Due to the potential risk of adverse reactions to SIRTURO® co-administered with nevirapine, or other moderate CYP3A4 inducers, should be avoided.

**QT Interval Prolonging Drugs**

Due to the potential risk of adverse reactions to SIRTURO®, lopinavir/ritonavir should be avoided with SIRTURO®. The risk of QT interval prolongation is increased in the presence of SIRTURO® and other QT interval prolonging drugs, such as azole antifungals, flecainide, and sotalol.

**Lopinavir/ritonavir**

Although clinical data in HIV/MDR-TB co-infected patients on the combined use of lopinavir/ritonavir (400 mg/larinavir 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.

**Efavirenz**

Concurrent administration of SIRTURO® and efavirenz, or other moderate CYP3A4 inducers, should be avoided.

**Available Data**

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.

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SIRTURO® Treatment Group</th>
<th>Placebo Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=79 n (%)</td>
<td>N=81 n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (38)</td>
<td>26 (32)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26 (33)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (28)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>14 (18)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>9 (11)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Transaminases increased*</td>
<td>7 (9)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (8)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Blood amylase increased</td>
<td>2 (3)</td>
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</table>

*Terms represented by “transaminases increased” included transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal.
Adverse Reactions

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

- 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.

Use SIRTURO® only in combination with other antimycobacterial drugs (see Dosage and Administration). Refer to the prescribing information of the drugs used in combination with SIRTURO® for their respective adverse reactions.

Clinical Studies Experience in Adults

Adverse drug 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. Eighty (79.0%) patients in the SIRTURO® group and 86 of 81 (99.8%) patients in the placebo treatment group were HIV-infected. Seven (8.9%) SIRTURO®-treated patients and 6 (74%) placebo-treated patients discontinued Study 1 because of an adverse reaction. No additional unique adverse reactions were identified from the uncontrolled Study 3.

In both Studies 1 and 2, alanine transaminase elevations of at least 3 times the upper limit of normal developed more frequently in the SIRTURO® treatment group (17/102 [16.7%] vs 6/105 [5.7%]) than in the placebo treatment group. In Study 3, 22/230 (9.6%) patients had alanine aminotransferase or aspartate aminotransferase 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 [1.1%, 18.2%]). Five of the 9 SIRTURO® deaths were tuberculosis-related. One additional SIRTURO® 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 129 days after last intake of SIRTURO®. The imbalance in deaths is unexplained; no discernible pattern between death and cause of death was observed in previously treated patients.

In the open-label Study 3, 6/273 (2.2%) 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 SIRTURO® is based on the Week 24 analysis of the single-arm, open-label trial, TMC207-C217, in 15 pediatric patients. The trial was designed to enroll patients 12 to less than 18 years of age (but only 14 to less than 18 years old were enrolled) with confirmed or probable pulmonary MDR-TB infection who received SIRTURO® at the recommended dosage regimen, in combination with a background regimen.

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®.

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

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*Terms represented as: 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.
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 Embryofetal 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 0.8, 2.5 and 9 times the clinical dose based on AUC comparisons) during the period of organogenesis (gestational Days 6-9, inclusive). No embryotoxic effects were found in rats or rabbits at dose exposures up 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 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 infants together with additional pharmacokinetic and safety data from the single-arm, open-label, trial that enrolled 15 pediatric patients 12 to less than 18 years of age with confirmed or probable MDR-TB infection who were treated with SIRTURO® for 24 weeks in combination with a background regimen. 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.

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.

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 0.01%). 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 for SIRTURO® when administered to patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis.

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 eliminated 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.

Pregnancy (Cont’d)

Risk Summary (Cont’d)

Pregnancy (Cont’d)

Pregnancy (Cont’d)

Pregnancy (Cont’d)

Pregnancy (Cont’d)

Table 2: Culture Conversion Status in Patients With MDR-TB at Week 24 and Week 120 in Study 1

<table>
<thead>
<tr>
<th>Microbiologic Status</th>
<th>SIRTURO® (24 weeks) + combination of other antimycobacterial drugs</th>
<th>Placebo (24 weeks) + combination of other antimycobacterial drugs</th>
<th>Difference (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum Culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure*</td>
<td>78%</td>
<td>58%</td>
<td>20.0% [4.5%, 35.6%] 0.04</td>
</tr>
<tr>
<td>Died</td>
<td>22%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Lack of conversion</td>
<td>21%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td><strong>Week 120</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum Culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure*</td>
<td>61%</td>
<td>44%</td>
<td>17.3% [5.1%, 34.0%] 0.046</td>
</tr>
<tr>
<td>Died</td>
<td>39%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Lack of conversion/ relapse</td>
<td>12%</td>
<td>3%</td>
<td>16%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>10%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

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 (ie, 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. 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 82 to the placebo arm. A final evaluation was conducted at Week 100.

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 analysis. Demographics were as follows: 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 486 cells/μL). Most patients had cavitation in one lung (62%) and 18% of patients had cavitation in both lungs.

Table 2 shows the proportion of patients with sputum culture conversion at Week 24 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 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 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 to culture conversion was 83 days for the SIRTURO® treatment group compared to 125 days for the placebo treatment group.
Pregnancy (Cont’d)

Risk Summary (Cont’d)
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 6-19, inclusive). Pregnant rabbits were treated with bedaquiline at 10, 30 and 100 mg/kg (approximately 0.5, 1.5 and 5 times the clinical dose based on AUC comparisons) during the period of organogenesis (gestational Days 6-9, 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 not 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 clinical need for SIRTURO® and any potential adverse effects. 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
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 12 to 18 years of age and in children with age less than 12 years 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 35 pediatric patients 14 to less than 18 years of age with confirmed or probable MDR-TB infection who were treated with SIRTURO® for 24 weeks in combination with a background regimen. 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.

The safety and effectiveness of SIRTURO® in pediatric patients less than 12 years of age and/or for weighing less than 30 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 0.01%); 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 tuberculosis. All patients received a combination of 6 other antimycobacterial drugs used to treat MDR-TB (ie, ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/ethionamide or available alternative) for a total duration of 18 to 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 12 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 80 to the placebo arm. A final evaluation was conducted at Week 120.

Hepatic 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 0.01%); 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.

Please see Important Safety Information, including Boxed Warnings, on pages 2-6.
**Adult Patients (Cont’d)**

**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.

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

The pediatric trial (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 MDR-TB infection. Fifteen patients ages 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 2 weeks and 200 mg 3 times/week for the following 22 weeks. In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with SIRTURO® resulted in a culture conversion rate of 75.0% (6/8 patients) at Week 24.

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

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For additional information, please visit [www.SIRTURO.com](http://www.SIRTURO.com).

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