WARNINGS:

• An increased risk of death was seen in the SIRTURO® (bedaquiline) treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO® when an effective treatment regimen cannot otherwise be provided.

• QT prolongation can occur with SIRTURO®. Use with drugs that prolong the QT interval may cause additive QT prolongation. 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 adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO® for use when an effective treatment regimen cannot otherwise be provided. SIRTURO® should be administered by directly observed therapy (DOT).

This indication is 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)
• Use SIRTURO® only in combination with other anti-mycobacterial 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® 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 (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® 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.

Hepatotoxicity
More hepatic-related adverse reactions were reported 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.

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 bedaquiline, 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]

Clinical Studies Experience

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

Adverse drug reactions for SIRTURO® were identified from the pooled safety data from 335 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, 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 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 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 subjects

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SIRTURO® Treatment Group N=79 n (%)</th>
<th>Placebo Treatment Group N=81 n (%)</th>
</tr>
</thead>
<tbody>
<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 (1)</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>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* Terms represented by ‘transaminases increased’ included transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal.
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) subjects died. The most common cause of death as reported by the investigator was TB (9 subjects). All but one subject who died of TB had not converted or had relapsed. The causes of death in the remaining subjects varied.

**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 bedaquiline 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 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 bedaquiline is required when co-administered with nevirapine.

**Efavirenz**

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

**QT Interval Prolonging Drugs**

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

In Study 3, mean increases in QTc were larger in the 17 subjects who were taking clofazimine with bedaquiline at Week 24 (mean change from reference of 31.9 ms) than in subjects who were not taking clofazimine with bedaquiline 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.

**Use in Specific Populations**

**Pregnancy**

Pregnancy Category B

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to bedaquiline. In these studies, the corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. There are, however, no adequate and well-controlled studies of SIRTURO® in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
**Nursing Mothers**

It is not known whether bedaquiline or its metabolites are excreted in human milk, but rat studies have shown that the drug is concentrated in breast milk. In rats treated with bedaquiline at doses 1 time to 2 times the clinical dose (based on AUC comparisons), concentrations in milk were 6-fold to 12-fold higher than the maximum concentration observed in maternal plasma. Pups from these dams showed reduced body weights compared to control animals throughout the lactation period.

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

**Pediatric Use**

The safety and effectiveness of SIRTURO® in pediatric patients 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 bedaquiline were assessed after single dose administration to subjects 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 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. Monitor 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**

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: 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 subjects’ baseline 
M. tuberculosis isolate obtained prior to randomization. The SIRTURO® treatment group had a 
decreased time to culture conversion and improved culture conversion rates compared to the placebo 
treatment group at Week 8. At Weeks 8 and 24, the differences in culture conversion proportions were 
38.9% (95% CI: [12.3%, 63.1%] and p-value: 0.004), 15.7% 
(95% CI: [-11.9%, 41.9%] and p-value: 0.32), respectively.

**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.

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 N=67 (%)</th>
<th>Placebo (24 weeks) + combination of other antimycobacterial drugs N=66 (%)</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>78%</td>
<td>58%</td>
<td>20.0% [4.5%, 35.6%] 0.014</td>
</tr>
<tr>
<td>Conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure*</td>
<td>22%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>1%</td>
<td>0%</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>61%</td>
<td>44%</td>
<td>17.3% [0.5%, 34.0%] 0.046</td>
</tr>
<tr>
<td>Conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure*</td>
<td>39%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>12%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Lack of conversion/</td>
<td>16%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>relapse</td>
<td></td>
<td></td>
<td></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.

Please see Important Safety Information, including Boxed Warnings, on pages 2-6.
For additional information, please visit www.SIRTURO.com.