1. **PRODUCT NAME**
SIRTURO™

2. **DOSAGE FORMS AND STRENGTHS**
SIRTURO™ 20 mg tablet
Each tablet contains 20 mg of bedaquiline free base (present as fumarate salt).
Oral tablet: uncoated, white to almost white oblong tablet with score line on both sides, debossed with "2" and "0" on one side and plain on other side.
For excipients, see List of Excipients.
SIRTURO™ 100 mg tablet
3. Each tablet contains 100 mg of bedaquiline free base (present as fumarate salt).
Oral tablet: uncoated, white to almost white round biconvex tablet with debossing of "T" over "207" on one side and "100" on the other side.
For excipients, see List of Excipients.

4 **CLINICAL INFORMATION**

4.1 **Indications**
Adult and Pediatric patients (5 years to less than 18 years of age)
SIRTURO™ is indicated in adult (≥ 18 years) and pediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant *Mycobacterium tuberculosis*.

4.2 **Dosage and Administration**
SIRTURO™ should only be administered as part of a multi-drug resistant tuberculosis (MDR-TB) regimen. It is recommended that SIRTURO™ is administered by directly observed therapy (DOT). MDR-TB is defined as *in vitro* resistance of the patient's isolate to at least isoniazid and rifampin.
The prescribing physician should refer to international (e.g. WHO guidelines) and national/local TB treatment guidelines for direction on selection and duration of use of companion drugs with SIRTURO™. SIRTURO™ should only be used in combination with at least 3 drugs to which the patient's isolate has been shown to be susceptible *in vitro*. If *in vitro* drug susceptibility testing results are unavailable, treatment may be initiated with SIRTURO™ in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible. SIRTURO™ can also be used as specified in the Prescribing Information of other drugs used for the treatment of MDR-TB.
Throughout treatment with, and following the last intake of SIRTURO™, patients should continue to take their companion drugs in accordance with international, national/local TB treatment guidelines and local MDR-TB treatment practice. Refer to the prescribing information of the drugs used in combination with SIRTURO™ for their specific dosing recommendations.
Dosage – Adults (≥18 years of age)
The recommended dosage of SIRTURO™ in adult patients is:
- Weeks 1-2: 400 mg once daily
- Weeks 3-24: 200 mg 3 times per week (with at least 48 hours between doses).

The total duration of treatment with SIRTURO™ is 24 weeks. SIRTURO™ should be taken with food.

Dosage –Pediatric patients (5 years to less than 18 years of age)

The recommended dosage of SIRTURO™ in pediatric patients (5 years to less than 18 years of age) is based on body weight and shown in Table 1.

Table 1: Recommended Dosage of SIRTURO™ in Pediatric Patients (5 years to less than 18 years of age)

Body Weight	Dosage Recommendation	
	Weeks 1 to 2	Weeks 3 to 24[a]
Greater than or equal to 15 kg to less than 30 kg	200 mg orally **once daily**	100 mg orally **three times per week**
Greater than or equal to 30 kg	400 mg orally **once daily**	200 mg orally **three times per week**

a=At least 48 hours between doses

The total duration of treatment with SIRTURO™ is 24 weeks. SIRTURO™ should be taken with food.

Missed dose(s)

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

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

From Week 3 onwards, if a dose is missed, patients should take the missed dose, and adjust the dosing schedule to ensure the total dose of SIRTURO™ during the 7 day period does not exceed the recommended weekly dose (with at least 24 hours between each intake).

Special populations

Pediatrics (less than 5 years of age)

The safety and efficacy of SIRTURO™ in children less than 5 years of age or weighing less than 15 kg have not been established.

Elderly (≥ 65 years of age)

There are limited clinical data on the use of SIRTURO™ in elderly patients.

Renal impairment

SIRTURO™ has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is insignificant (< 0.001%). No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis, SIRTURO™ should be used with caution (see *Pharmacokinetic Properties – Renal impairment*).

Hepatic impairment

The pharmacokinetics of bedaquiline were assessed after single-dose administration to subjects with moderate hepatic impairment (Child-Pugh B) (see *Pharmacokinetic*

Properties – Hepatic impairment). Based on these results, no dose adjustment is necessary for SIRTURO™ in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population.

Administration

SIRTURO™ should be taken orally with food, as administration with food increases oral bioavailability (see *Pharmacokinetic Properties – Absorption*). There are four different options for administration of SIRTURO™ 20 mg tablet and one method of administration of SIRTURO™ 100 mg tablet. Each administration method requires SIRTURO™ to be taken with food.

SIRTURO™ 20 mg tablet

*Administration of 20 mg Tablets to Patients who **Can** Swallow Intact Tablets:*

SIRTURO™ 20 mg tablet should be swallowed whole, or in two equal halves divided along the functional score line, with water and taken with food.

*Administration of 20 mg Tablets to Patients who **Cannot** 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 product, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g., yoghurt, 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 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 Feeding Tube

SIRTURO™ 20 mg tablet can also be administered through a feeding 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 feeding 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 feeding tube.

SIRTURO™ 100 mg tablet

SIRTURO™ 100 mg tablet should be swallowed whole with water.

4.3 Contraindications

None known.

4.4 Warnings and Precautions

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

Resistance to bedaquiline

Bedaquiline must only be used in an appropriate combination regimen for MDR-TB treatment as recommended by official guidelines, such as from WHO, to reduce the risk of development of resistance to bedaquiline.

Mortality

In the 120-week C208 trial in adults where SIRTURO™ was administered for 24 weeks in combination with a background regimen, more deaths occurred in the SIRTURO™ treatment group than in the placebo group (see *Adverse Reactions*). After enrollment, 12.7% (10/79) patients died in the SIRTURO™ treatment group (N = 79) compared to 3.7% (3/81) patients in the placebo group (N = 81). One death occurred during administration of SIRTURO™. The median time to death for the remaining nine patients was 344 days after last intake of SIRTURO™. One of the ten deaths in the SIRTURO™ treatment group and one of the 3 deaths in the placebo group occurred after the Week 120 window. In the SIRTURO™ treatment group, the most common cause of death as reported by the investigator was TB (5 patients). The causes of death in the remaining SIRTURO™ patients varied. The imbalance in deaths is unexplained. In addition, no discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, human immunodeficiency virus (HIV) status, or severity of disease was observed. For additional information on deaths in the C209 trial, see *Adverse Reactions*.

Cardiovascular safety

During clinical trials in adults with SIRTURO™ a prolongation of QTc interval was observed (see *Adverse Reactions*). An ECG should be obtained prior to and after initiation of therapy with SIRTURO™ to monitor the QTc interval. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected.

SIRTURO™ treatment initiation is not recommended in patients with:

- Heart failure,

- QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat ECG), or
- A personal or family history of congenital QT prolongation
- A history of or ongoing hypothyroidism
- A history of or ongoing bradyarrhythmia
- A history of Torsade de Pointes

If necessary, bedaquiline treatment initiation could be considered in these patients after a favorable benefit risk assessment and with frequent ECG monitoring.
SIRTURO™ treatment must be discontinued if the patient develops:
- Clinically significant ventricular arrhythmia
- A QTcF interval of > 500 ms (confirmed by repeat ECG)

An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other drugs that prolong the QT interval (including delamanid) cannot be excluded (see *Interactions*). Caution is recommended when prescribing bedaquiline concomitantly with medications with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.
Concomitant administration of SIRTURO™ with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin and sparfloxacin) should be avoided.
In an open label Phase 2b trial (C209) in adults, mean increases from baseline in QTcF were larger in subjects with concomitant clofazimine use than in subjects without concomitant clofazimine use (see *Interactions*). In the event that co-administration of clofazimine with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

Hepatic safety

Increases in transaminases or aminotransferase elevations accompanied by total bilirubin ≥ 2x ULN were seen in clinical trials in adult and pediatric patients during administration of SIRTURO™ with the background regimen (see *Adverse Reactions*). Patients should be monitored during treatment. If AST or ALT exceeds 5 times the upper limit of normal then the regimen should be reviewed and SIRTURO™ and/or any hepatotoxic background drug should be discontinued.
Other hepatotoxic drugs and alcohol should be avoided while on SIRTURO™, especially in patients with diminished hepatic reserve.

Drug interactions

CYP3A4 inducers/inhibitors

Bedaquiline is metabolized by CYP3A4 and its exposure may therefore be reduced during co-administration with inducers of CYP3A4 and increased during co-administration with inhibitors of CYP3A4 (see *Interactions*).
Co-administration of bedaquiline and drugs that induce CYP3A4 may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Co-administration of strong CYP3A4 inducers, such as rifamycins (i.e., rifampin, rifapentine and rifabutin), or moderate CYP3A4 inducers used systemically, such as efavirenz, should therefore be avoided during treatment with SIRTURO™.

Co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided.

HIV-TB co-infected patients

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

Interactions

CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2).

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

CYP3A4 inducers/inhibitors

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

In an interaction study of single-dose bedaquiline and once daily rifampin in healthy adult subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of bedaquiline due to a decrease in systemic exposure, co-administration of strong CYP3A4 inducers, such as rifamycins (i.e., rifampin, rifapentine and rifabutin), or moderate CYP3A4 inducers used systemically, such as efavirenz, should be avoided during treatment with SIRTURO™.

The short-term co-administration of bedaquiline and ketoconazole in healthy adult subjects increased the exposure (AUC) to bedaquiline by 22% [90% CI (12; 32)]. Due to the potential risk of adverse reactions due to an increase in systemic exposure, prolonged co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided.

Other antimicrobial medications

The short-term co-administration of bedaquiline with isoniazid/pyrazinamide in healthy adult subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with SIRTURO™. In a placebo-controlled clinical study 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

In an interaction study of single-dose bedaquiline and multiple-dose lopinavir/ritonavir in adults, exposure (AUC) to bedaquiline was increased by 22% [90% CI (11; 34)]. Clinical data on the combined use of lopinavir/ritonavir and SIRTURO™ in HIV/MDR-TB

co-infected patients are not available (see *Warnings and Precautions*). If the benefit outweighs the risk, SIRTURO™ may be used with caution when co-administered with lopinavir/ritonavir.

Nevirapine

Co-administration of multiple-dose nevirapine in adults did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on the combined use of nevirapine and SIRTURO™ in HIV/MDR-TB co-infected patients are not available (see *Warnings and Precautions*).

QT interval prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline and drugs that prolong the QT interval. In an interaction study of bedaquiline and ketoconazole in adults, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual drugs. An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other drugs that prolong the QT interval cannot be excluded (see *Warnings and Precautions*).

QT interval and concomitant clofazimine use

In an open label Phase 2b trial in adults, mean increases in QTcF were larger in the 17 subjects who were using concomitant clofazimine at Week 24 (mean change from reference of 31.9 ms) than in subjects who were not using concomitant clofazimine at Week 24 (mean change from reference of 12.3 ms) (see *Warnings and Precautions*).

4.5 Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies with SIRTURO™ in pregnant women. At clinically relevant exposures, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see *Non-Clinical Information*). As a precautionary measure, it is recommended to avoid the use of SIRTURO™ during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Breast-feeding

It is not known whether bedaquiline or its metabolites are excreted in human milk.

In rats, concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period (see *Non-Clinical Information*).

Because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from SIRTURO™ therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No human data on the effect of bedaquiline on fertility are available. In female rats, there was no effect on mating or fertility with bedaquiline treatment. Three of 24 male rats treated with high bedaquiline doses failed to produce offspring in the fertility study. Normal spermatogenesis and a normal amount of spermatozoa in the epididymides were

noted in these animals. No structural abnormalities in the testes and epididymides were seen after up to 6 months of bedaquiline treatment (see *Non-Clinical Information*).

4.6 **Effects on Ability to Drive and Use Machines**

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

4.7 **Adverse Reactions**

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of bedaquiline based on the comprehensive assessment of the available adverse event information. A causal relationship with bedaquiline cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Refer to the prescribing information of the drugs used in combination with SIRTURO™ for their respective adverse reactions.

4.8 ***Adverse reactions from clinical trials in adult patients***

Adverse drug reactions (ADRs) for SIRTURO™ were identified from pooled Phase 2b clinical trial data (both controlled and uncontrolled) containing 335 patients who received SIRTURO™ in combination with a background regimen of TB drugs. The basis of assessment of causality between the ADRs and SIRTURO™ was not restricted to these trials but also on review of the pooled Phase 1 and Phase 2a safety data.

The most frequent ADRs (> 10.0% of patients) during treatment with SIRTURO™ in the controlled trials were nausea, arthralgia, headache, vomiting and dizziness.

Adverse drug reactions to SIRTURO™ are presented in Table 2. Adverse drug reactions are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

Table 2: All Adverse Drug Reactions from Controlled Trials in Adults During Treatment with SIRTURO™

Adverse Drug Reactions	**Frequency**	**SIRTURO™ N=102** ***n (%)***	**Placebo N=105** ***n (%)***
Nervous system disorders			
Headache	Very Common	24 (23.5)	12 (11.4)
Dizziness	Very Common	13 (12.7)	12 (11.4)
Cardiac disorders			
ECG QT prolonged	Common	3 (2.9)	4 (3.8)
Gastrointestinal disorders			
Nausea	Very Common	36 (35.3)	27 (25.7)
Vomiting	Very Common	21 (20.6)	24 (22.9)
Diarrhea	Common	6 (5.9)	12 (11.4)
Hepatobiliary disorders			

Transaminases Increased*	Common	7 (6.9)	1 (1.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	Very Common	30 (29.4)	21 (20.0)
Myalgia	Common	6 (5.9)	7 (6.7)

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

No additional ADRs were identified in adult patients from the uncontrolled study C209 (N = 233) nor from the Phase 1 and 2a studies.

Deaths

In the C208 trial in adult patients, there were more deaths reported in the SIRTURO™ treatment group (see *Warnings and Precautions*). In the SIRTURO™ treatment group, the most common cause of death as reported by the investigator was TB (5 patients). All of the deaths due to TB occurred in patients whose sputum culture status at last visit was 'not converted'. The causes of death in the remaining SIRTURO™ patients varied. In addition, the imbalance in deaths is unexplained; no discernible pattern between death and sputum conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, and severity of disease was observed.

During the trial, there was no evidence of antecedent significant QTcF prolongation or clinically significant dysrhythmia in any of the patients that died. See Table 3 for a summary of deaths in the C208 trial.

Table 3: Summary of Deaths During the C208 Trial in Adults

SIRTURO™/BR Group			
Cause of Death	**Duration of Exposure* (days)**	**Days Since Last Study Drug Intake**	**Sputum Culture Status at Last Visit**
Tuberculosis‡	168	344	not converted
Tuberculosis‡	163	281	not converted
Tuberculosis-related illness§	29	787	not converted
Tuberculosis-related illness§	168	262	not converted
Tuberculosis-related illness§	90	314	not converted
Alcohol poisoning#	109	2	converted
Hepatitis/hepatic cirrhosis‡	168	86	converted
Septic shock/peritonitis‡	170	513	converted
Cerebrovascular accident‡	168	556	converted
Motor vehicle accident§	142	911	not converted
Placebo/BR Group			

Cause of Death	Duration of Exposure* (days)	Days Since Last Study Drug Intake	Sputum Culture Status at Last Visit
Hemoptysis‡	168	105	not converted
Tuberculosis-related illness§	165	709	not converted
Tuberculosis-related illness	128	1048	converted

BR = background regimen of multidrug resistant tuberculosis medication consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone

* the duration of exposure refers to blinded study drug administration

‡ died after the end of the investigational period

§ died after prematurely discontinuing from the trial

\# died during the investigational period when SIRTURO™ was administered

In the open-label C209 trial in adult patients, 6.9% (16/233) of 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.

Cardiovascular safety

In the controlled Phase 2b study (C208) in adult patients, mean increases in QTcF were observed from the first on-treatment assessment onwards (9.9 ms at Week 1 for SIRTURO™ and 3.5 ms for placebo). The largest mean increase in QTcF during the 24 weeks of SIRTURO™ treatment was 15.7 ms (at Week 18). After the end of SIRTURO™ treatment (i.e. after Week 24), QTcF increases in the SIRTURO™ group gradually became less pronounced. The largest mean increase in QTcF in the placebo group during the first 24 weeks was 6.2 ms (at Week 18) (see *Warnings and Precautions*).

Adverse reactions from clinical trial in pediatric patients (5 years to less than 18 years of age)

The safety assessment of bedaquiline is based on the Week 24 analysis of the single-arm, open-label, multi-cohort, Phase 2 trial (C211) in 30 pediatric patients.

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

The trial was designed to enroll patients from 12 years to less than 18 years of age (15 patients aged 14 years to less than 18 years were enrolled) with confirmed or probable 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 (see *Pharmacological properties – Clinical Studies*).

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

to those in adults. No new adverse drug reactions were identified compared to those seen in adults.

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

The trial was designed to enroll patients from 5 years to less than 12 years of age (15 patients aged 5 years to less than 11 years were enrolled) with confirmed or probable 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 (see *Pharmacological properties – Clinical Studies*).

The most common adverse drug reactions were related to elevations in liver enzymes (5/15, 33%), reported as ALT/AST increased and hepatotoxicity; hepatoxicity led to discontinuation of SIRTURO™ in three patients. Elevations in liver enzymes were reversible upon discontinuation of SIRTURO™ and background regimen. Among these 15 pediatric patients, no deaths occurred during treatment with SIRTURO™.

4.9 Overdose

Symptoms and signs

Cases of intentional or accidental acute overdose with bedaquiline were not reported during clinical trials. In a study in 44 healthy adult subjects receiving a single 800 mg dose of SIRTURO™, adverse reactions were consistent with those observed in clinical studies at the recommended dose (see *Adverse Reactions*).

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK05

Bedaquiline is a diarylquinoline with *in vitro* activity against drug-sensitive TB (DS-TB), MDR-TB including pre-extensively drug resistant (pre-XDR-TB) and XDR-TB. Pre-XDR TB is defined as *in vitro* resistance of the patient's isolate to: (1) isoniazid, (2) rifampin and (3) either a fluoroquinolone or at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin). XDR-TB is defined as *in vitro* resistance of the patient's isolate to: (1) isoniazid, (2) rifampin, (3) a fluoroquinolone and (4) at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Mechanism of action

Bedaquiline is a diarylquinoline with a novel mechanism of action. Bedaquiline specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The

inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Bedaquiline demonstrates high selectivity for mycobacterial (prokaryotic) ATP synthase as opposed to mammalian (eukaryotic) ATP synthase. Bedaquiline has very low activity for human ATP synthase in mitochondria (IC_{50} > 100 μM), resulting in a selectivity index of > 10000 compared to the mycobacterial ATP synthase (IC_{50} 0.01 μM).

5.2 Pharmacodynamic effects

Bedaquiline has activity against *M. tuberculosis* with a minimal inhibitory concentration (MIC) for drug sensitive as well as drug resistant strains (MDR-including pre-XDR-, XDR-strains) in the range of ≤ 0.008-0.12 micrograms/mL. Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of *N*-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (3- to 6-fold lower) compared to the parent compound.

The intracellular bactericidal activity of bedaquiline in primary peritoneal macrophages and in a macrophage-like cell line was greater than its extracellular activity. Bedaquiline is also bactericidal against dormant (non-replicating) tubercle bacilli. In the mouse model for TB infection, bedaquiline has demonstrated bactericidal and sterilizing activities.

Microbiology

Mechanisms of resistance

Acquired resistance mechanisms that affect bedaquiline MICs include mutations in the *atpE* gene, coding for the ATP synthase target, and in the *Rv0678* gene, regulating the expression of the MmpS5-MmpL5 efflux pump. Target-based mutations generated in preclinical studies lead to 8- to 133-fold increases in bedaquiline MIC, resulting in MICs ranging from 0.25 to 4 micrograms/mL. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to 2- to 8-fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0.25 to 0.5 micrograms/mL. The majority of isolates that are phenotypically resistant to bedaquiline are cross-resistant to clofazimine. Isolates that are resistant to clofazimine can still be susceptible to bedaquiline.

The impact of high baseline bedaquiline MICs, the presence of *Rv0678* based mutations at baseline, and/or increased post-baseline bedaquiline MICs on microbiologic outcomes is unclear because of the low incidence of such cases in the Phase 2 trials.

For further information on bedaquiline MICs in clinical studies, see *Pharmacodynamic Properties – Clinical studies*.

Lists of microorganisms

Bedaquiline has been shown to be active against most isolates of *Mycobacterium tuberculosis*, both *in vitro* and in clinical infections (see *Indications*).

Susceptibility test methods

When available, the clinical microbiology laboratory should provide the physician with the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting a combination of antibacterial drug products for treatment.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of mycobacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method, agar or 7H9 broth microdilution or equivalent with standardized inoculum concentrations and standardized concentrations of bedaquiline (see below). The MIC values should be interpreted according to the criteria provided in Table 4.

Method for bedaquiline minimal inhibitory concentration determination in 7H11 or 7H10 agar medium[ab]

A 200 micrograms/mL working solution is made in dimethylsulfoxide (DMSO) and used to prepare 2-fold serial dilutions in DMSO (from 200 micrograms/mL to 0.8 micrograms/mL). These 100x working solutions are then diluted 1/100 in 7H11 or 7H10 agar medium to obtain the final CLSI concentrations of 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015 and 0.008 micrograms/mL.

MTB isolates are grown on 7H11 or 7H10 medium (or Lowenstein-Jensen medium). A rack should be prepared with all the tubes needed for the MTB isolate. On the first control tube, the date of inoculation is written. The required number of dilution tubes is filled with the appropriate amount of sterile distilled water. The culture number is provided on a 5 mL Bijoux bottle and sterile glass beads added as per local procedure. Absorbent paper is placed on the working area of the safety cabinet and soaked with 10% Dettol from the wash bottle. All manipulations are performed above this wet paper to avoid spattering of falling drops.

A suspension with turbidity equal to a McFarland standard 1 is prepared by scraping several loops full (2 to 5 mg) of growth from drug-free medium. Attempt should be made to pick a portion from each colony. The mycobacteria are transferred to a sterile 16 x 125 mm screw cap tube containing 6 to 8 glass or plastic beads and a few drops of Tween-albumin liquid medium. The suspension is homogenized on a test tube mixer for 5 to 10 minutes and larger particles allowed to settle. The supernatant suspension is withdrawn and density adjusted to that of a McFarland standard 1 (~5 x 10^7 colony-forming units (CFU)/mL) with sterile distilled water or saline.

Make serial 10-fold dilutions in sterile distilled water or saline. Using a new pipette, mix the suspension of the undiluted (10^0) tube (~5 x 10^7 CFU/mL) and transfer 0.1 mL to 0.9 mL of the first dilution tube (10^{-1}) (~5 x 10^6 CFU/mL). Inoculate the 7H10 or 7H11 agar tubes or plate containing bedaquiline with 0.1 mL of the 10^{-1} dilution leading to 5 x 10^5 CFU plated.

Using a new pipette, additional 10-fold serial dilutions (10^{-3}, 10^{-4} and 10^{-5}) are made from the 10^{-1} dilution tube. Control 7H10 or 7H11 tubes or plates are inoculated with 0.1 mL

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[a] Canetti G, Froman S, Grosset J. *et al*. Mycobacteria: Laboratory Methods for Testing Drug Sensitivity and Resistance. Bull. Wld Hlth Org. 1963; 29: 565-578.

[b]CLSI. Susceptibility testing of Mycobacteria, Nocardieae, and other aerobic Actinomycetes; Approved Standards-Second Edition. CLSI Document M24-A2. Wayne, PA: Clinical and Laboratory Standards Institute. Available at *www.iso90.ir/phocadownload/csli/M24-A.pdf.*

of 10^{-3}, 10^{-4} and 10^{-5} dilutions. This should lead to 5000 CFU/plate, 500 CFU/plate and 50 CFU/plate, respectively. It is important to well standardize the size of the inocula since the results are influenced by them. The inoculum size should be within 0.5 log of the target to accept the MIC as valid.

Tubes are incubated inclined overnight at room temperature (making sure that the solution is covering the whole surface of the tubes). Next day, the tubes are incubated standing at 35ºC to 37ºC + 4% to 5% CO_2 (at least for one week, loose caps). For plates, lid cover should be maintained in the upward position for 1 to 2 days inside the incubator at 35ºC to 37ºC until the inoculum is dry. Then the plates are turned upside down.

Note:

Once the tubes/plates are dry, they should be put in a plastic bag if the incubator is dry (no water). If the incubator used is a wet incubator (contains water), no need to put the tubes/plates in a plastic bag.

Report results at 21 days post-inoculation. The MIC will be assessed as the lowest drug concentration that results in complete inhibition of growth.

It is important to have fresh growth on a solid medium (21-28 days old). Older cultures may result in unreliable susceptibility test results. Drug solutions in DMSO may be frozen in aliquots at -20°C and stored for up to 3 months. Once thawed, discard the leftover and do not store or refreeze. The solid medium should be 7H11 or 7H10 agar (not Lowenstein-Jensen), and the plate/tube should be polystyrene (not polypropylene).

For bedaquiline MIC determinations, a quality control is performed by testing the MTB H37Rv strain (ATCC-American Type Culture Collection-number 27294), a susceptible strain to bedaquiline, on each new lot of 7H11 or 7H10 agar using the same set of concentrations used in the assay for the MTB isolates. Standard bedaquiline solutions should provide the following range of MIC values: 0.015 to 0.12 micrograms/mL.

Method for bedaquiline minimal inhibitory concentration determination using 7H9 broth medium[c]

A 400 micrograms/mL working solution is made in DMSO and 2-fold serial dilutions are made from 400 micrograms/mL to 1.6 micrograms/mL in DMSO. These working solutions are then diluted 1/100 in 7H9 medium to obtain 2x drug concentrations of 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03 and 0.015 micrograms/mL.

M. tuberculosis isolates are grown on 7H11 medium (or Lowenstein-Jensen). Colonies are subcultured in Middlebrook 7H9 broth supplemented (7H9-S) with 10% (oleic acid, albumin, dextrose, and catalase), 0.5% glycerol and 0.1% casitone for 7 days at 37°C. The turbidity of the resulting suspension is adjusted with phosphate-buffered saline (PBS) to match that of a McFarland standard 1 suspension which corresponds to ~5 x 10^7 CFU/mL of microorganisms. Using a calibrated micropipeting device, prepare 2x inoculum by inoculating 14.7 mL of 7H9-S tube with 300 µL of the 1 McFarland suspensions (50-fold dilution from 1 McFarland or 1 x 10^6 CFU/mL).

A 100 µl of 2x bedaquiline working solutions is added to wells except the growth control wells which receive 100 µl 7H9-S only. Using a disposable inoculum reservoir pour the

[c] Martin A, Camacho M, Portaels F, and Palomino JC. Resazurin microtiter assay plate testing of Mycobacterium tuberculosis: susceptibilities to second-line drugs: rapid, simple, and inexpensive method. Antimicrob Agents Chemother. 2003; 47: 3616-3619.

2x inoculum into the reservoir. Using an 8 or 12 channel micro-pipette and sterile tips with filters, 100 µl of 2x inoculum 1 x 10^6 CFU/mL in 7H9-S broth is added to all microtiter wells including the growth control well but not in the well containing the negative control. At this point the final drug concentrations are 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015 and 0.008 micrograms/mL and the inoculum size is 5 x 10^5 CFU/mL. After inoculation, the plates are sealed in plastic bags and incubate at 35ºC to 37ºC.
Read MICs at Day 7, Day 10 and Day 14. No more reading should occur after Day 14. For better interpretation of the results, growth must be compared to that of the control (positive) well. Microtiter plates should be read by visual inspection per local procedure. The MIC of each drug is interpreted as the lowest concentration of the antibiotic that completely prevents visual growth. The positive control should show positive growth and the negative control should show no growth within the incubation protocol period. If the negative control shows a growth, the procedures need to be investigated for potential cross-manipulation and all reagents checked for possible source of contamination.
Note:
The 7H9-S medium should be stored protected from light at 4°C.
It's important to have fresh growth on a solid medium (21-28 days old). Older cultures may result in unreliable susceptibility test results. Drug solutions in DMSO may be frozen in aliquots at -20°C and stored for up to 3 months. Once thawed, discard the leftover and do not store or refreeze. The test plate should be in polystyrene.
The incidence of contamination varies from laboratory to laboratory depending of several factors. The recommendation is that up to 5% contamination rate is acceptable. Liquid media are more susceptible to contamination than solid media. It is extremely important to take care during the manipulation and to work with sterile material. Any well with a turbid appearance is suspected of contamination and result of this well is not valid.

Table 4. Susceptibility Test Result Interpretive Criteria for Bedaquiline

Pathogen	Minimal Inhibitory Concentration (micrograms/mL)	
	7H11 Agar*	REMA‡ (7H9 broth)
	Susceptible Only (S)	Susceptible Only (S)
M. tuberculosis	≤ 0.5	≤ 0.25

* Studies using 7H11 agar only
‡ Studies using resazurin microtiter assay (REMA) only

A report of Susceptible indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. Isolates with MICs above the susceptible breakpoint may not indicate the presence of a resistance mechanism. The minimal inhibitory concentration of the isolate in the non-susceptible range may be within the previously recognized wild-type distribution of susceptibility results; however, there is limited experience with these isolates in clinical trials.

Quality control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. For bedaquiline MIC determinations, a quality control is performed by testing the *M. tuberculosis* H37Rv

strain (ATCC-American Type Culture Collection-number 27294), a susceptible strain to bedaquiline, on each new lot of 7H11 agar and 7H9 broth using the same set of concentrations used in the assay for the MTB isolates. Standard bedaquiline solutions should provide the following range of MIC values noted in Table 5.

Table 5. Acceptable Quality Control Ranges for Bedaquiline

	Recommended Bedaquiline MIC (micrograms/mL)		
QC Organism	7H9 broth	7H10 Agar	7H11 Agar
M. tuberculosis H37Rv	0.015 – 0.06	0.015 – 0.12	0.015 – 0.12

Pharmacokinetic/pharmacodynamic relationship

The area under the plasma concentration-time curve has been shown to best correlate with efficacy in a mouse model of TB infection.

Effect on QT/QTc interval and cardiac electrophysiology

The effect of a single supratherapeutic bedaquiline 800 mg dose on QTc interval was evaluated in a double-blind, randomized, placebo-, and positive-controlled (moxifloxacin 400 mg) parallel group QT study in 44 healthy adult subjects. The placebo-adjusted maximum mean increase in QTcF was 5.2 ms, 90% confidence interval [CI]: [1.5, 8.9]). The upper limit of the 90% CI was below the threshold of 10 ms indicating that this thorough QT study did not reveal a clinically significant effect of bedaquiline on the QT interval. Trial (assay) sensitivity was demonstrated with moxifloxacin.

However, an increase in QTcF when using SIRTURO™ was demonstrated in the Phase 2 studies in adults (see *Warnings and Precautions*).

Clinical studies

Adult patients

A Phase 2b, placebo controlled, double blind, randomized trial (C208) was conducted to evaluate the antibacterial activity, safety, and tolerability of SIRTURO™ in newly diagnosed patients with sputum smear-positive pulmonary MDR-TB including patients with pre-XDR-TB. Patients were randomized to receive treatment with either SIRTURO™ (n = 79) or placebo (n = 81) for 24 weeks in combination with a preferred 5-drug background regimen of MDR-TB medication consisting of ethionamide (ETH), kanamycin (KAN), pyrazinamide (PZA), ofloxacin (OFL), and cycloserine/terizidone. After the 24-week investigational period, the background regimen was continued to complete 18 to 24 months of total MDR-TB treatment. A final evaluation was conducted at Week 120. Main demographics were as follows: 63.1% of the study population was male, with a median age of 34 years, majority (35% [n = 56]) were Black and 15% (n = 24) patients were HIV positive. Most patients had cavitation in one lung (57.5%); cavitation in both lungs was observed in 16.3% of patients. Of the primary efficacy analysis population, 111 patients had isolates with full characterization of resistance status. 75.7% (84/111) of patients were infected with an MDR-TB strain and 24.3% (27/111) were infected with a pre-XDR-TB strain.

SIRTURO™ was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times/week for the following 22 weeks. After the double-blind treatment phase patients

continued to receive their background MDR-TB treatment until a total treatment duration of 18 to 24 months was achieved, or at least 12 months after the first confirmed negative culture.
The primary outcome parameter was the time to sputum culture conversion (i.e. the interval in days between the first SIRTURO™ intake and the date of the first of two consecutive negative liquid cultures from sputum collected at least 25 days apart) during treatment with SIRTURO™ or placebo.
The addition of SIRTURO™ to a preferred background regimen of MDR-TB treatment resulted in a decreased time to culture conversion and improved culture conversion rates compared to placebo. Median time to culture conversion according to the primary analysis method was 83 days for the SIRTURO™ group compared to 125 days for the placebo group ($p < 0.0001$; hazard ratio, 95% CI: 2.44 [1.57; 3.80]). The proportion of patients in the modified intent-to-treat (mITT) population with sputum culture conversion after 24 weeks of treatment with SIRTURO™ or placebo in combination with background regimen (with patients who discontinued considered as non responders), was 52/66 (78.8%) in the SIRTURO™ group and 38/66 (57.6%) in the placebo group. In the SIRTURO™ group, no or only minor differences in time to culture conversion and culture conversion rates were observed between patients with pre-XDR-TB and patients with MDR-TB resistant to only rifampin and isoniazid. The rates of culture conversion in patients with MDR-TB resistant to only rifampin and isoniazid were 82.1% (32/39) in the SIRTURO™ group and 62.2% (28/45) in the placebo group. In addition, in the subgroup of patients infected with a pre-XDR-TB strain, a higher rate of culture conversion was seen in the SIRTURO™ group [73.3% (11/15)] vs. the placebo group [33.3% (4/12)].
Durability of response seen in the SIRTURO™ treatment group was supported by the results as shown below. The proportion of responders (with patients who discontinued considered as non responders) at Week 120 was 41/66 (62.1%) in the SIRTURO™ group and 29/66 (43.9%) in the placebo group.

Table 6: Culture Conversion Status		
Culture Conversion Status, n (%)	mITT population	
	SIRTURO™/BR N = 66	Placebo/BR N = 66
Overall responder at Week 24	52 (78.8%)	38 (57.6%)
Overall non-responder* at Week 24	14 (21.2%)	28 (42.4%)
Overall responder at Week 120	41 (62.1%)	29 (43.9%)
Overall non-responder* at Week 120	25 (37.9%)	37 (56.1%)
Failure to convert	*8 (12.1%)*	*15 (22.7%)*
Relapse†	*6 (9.1%)*	*10 (15.2%)*
Discontinued but converted	*11 (16.7%)*	*12 (18.2%)*

mITT = modified intent-to-treat; BR = background regimen

* Patients who died during the trial or discontinued the trial were considered as non-responders

† Relapse was defined in the trial as having a positive sputum culture after or during treatment following prior sputum culture conversion.

A Phase 2b, open label trial (C209) was conducted 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. Main demographics were as follows: 64% of the study population was male, median age 32, majority were Asian (39%) or Black (32%) and 11 patients (5%) were HIV positive. About half of the patients (51.9%) had cavitation in only one lung; 11.6% had cavitation in both lungs and 36.5% had no cavitation. Of the primary efficacy analysis population, 174 patients had isolates with full characterization of resistance status. 53.4% (93/174) of patients were infected with an MDR strain, 25.3% (44/174) of patients were infected with a pre-XDR strain, and 21.3% (37/174) of patients were infected with an XDR strain.

Patients received SIRTURO™ for 24 weeks in combination with an individualized background regimen of antibacterial drugs: fluoroquinolones [89.3%; mainly ofloxacin: (52.4%) and levofloxacin: (30.5%)], pyrazinamide (76.0%), aminoglycosides (72.1%; mainly kanamycin: 50.2%), and ethambutol (51.9%). Other baseline background regimen drugs taken by > 40% of patients were PAS C (46.4%) and ethionamide (42.1%). SIRTURO™ was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times/week for the following 22 weeks. Upon completion of the 24 week treatment with SIRTURO™, all patients continued to receive their background regimen in accordance with national/local TB program (NTP) treatment guidelines. A final evaluation was conducted at Week 120.

The primary efficacy endpoint was the time to sputum culture conversion during treatment with SIRTURO™. Median time to sputum culture conversion excluding patients with drug–sensitive TB (DS-TB) and those that did not have a positive sputum culture at screening and/or baseline (mITT; 205 patients), was 57 days. At Week 24, 163 of 205 (79.5%) patients responded to SIRTURO™ treatment as determined by sputum culture conversion rates. Conversion rates at Week 24 were highest (87.1%;

81/93) in patients with MDR-TB resistant to only rifampin and isoniazid, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients.
At Week 120, 148 of 205 (72.2%) patients responded to SIRTURO™ treatment as determined by sputum culture conversion rates. Conversion rates at Week 120 were highest (73.1%; 68/93) in patients with MDR-TB resistant to only rifampin and isoniazid, 70.5% (31/44) in pre-XDR-TB patients and lowest (62.2%; 23/37) in XDR-TB patients.
At both Week 24 and Week 120, responder rates were higher for patients on 3 or more active drugs (*in vitro*) in their background regimen.
Of the 163 patients who were responders at Week 24, 139 patients (85.3%) were still responders at Week 120. Twenty-four of these 24-week responders (14.7%) were considered non-responders at Week 120, of which 19 patients had prematurely discontinued the trial while being culture converted and 5 patients had experienced relapse. Of the 42 patients who were non-responders at Week 24, confirmed culture conversion after Week 24 (i.e., after bedaquiline dosing ended but the background regimen was continued) occurred in 9 patients (21.4%) and was maintained at Week 120.
Although there were differences in background regimens used across trials, safety results were generally similar between trials C208 and C209.
No clear relationship between increased post-baseline bedaquiline MIC and microbiologic outcome was observed in these trials where bedaquiline was given for 24 weeks, followed by continuation of the background regimen. For further information on bedaquiline mechanisms of resistance, see *Pharmacodynamic Properties – Mechanisms of resistance*.
Pediatric patients (5 years to less than 18 years of age)
The pharmacokinetics, safety and tolerability of SIRTURO™ in combination with a background regimen were evaluated in trial C211, a single-arm, open-label, multi-cohort Phase 2 trial that was designed to enroll 30 pediatric patients 5 years to less than 18 years of age with confirmed or probable MDR-TB infection who were to complete at least 24 weeks of treatment.
Pediatric patients (12 years to less than 18 years of age)
Fifteen adolescent patients were 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. These 15 patients had a median age of 16 years (range: 14-17), weighed 38 kg to 75 kg, and were 80% female, 53% Black, 33% White and 13% Asian.
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% (6/8 microbiologically evaluable patients) at week 24.
Pediatric patients (5 years to less than 12 years of age)
Fifteen pediatric patients were enrolled in this cohort. 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. These 15 patients had median age of 7 years (range: 5-10), weighed 14 kg to 36 kg, and were 60% female, 60% Black, 33% White and 7% Asian.

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 microbiologically evaluable patients) at Week 24.

Pharmacokinetic Properties

Absorption

After oral administration bedaquiline is well absorbed. Maximum plasma concentrations (C_{max}) are typically achieved at about 5 hours post dose. C_{max} and the area under the plasma concentration time curve (AUC) increased proportionally up to the highest doses studied (700 mg single-dose and once daily 400 mg multiple doses). Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. Therefore, bedaquiline should be taken with food to enhance its oral bioavailability.

Distribution

The plasma protein binding of bedaquiline is > 99.9% in all species tested, including human. In animals, bedaquiline and its active *N*-monodesmethyl metabolite (M2) are extensively distributed to most tissues, however, brain uptake was low.

Metabolism

CYP3A4 was the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2).

Excretion

Based on preclinical studies, bedaquiline is mainly eliminated in feces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant. After reaching C_{max}, bedaquiline concentrations decline tri-exponentially. The mean terminal elimination half-life of bedaquiline and the active *N*-monodesmethyl metabolite (M2) is about 5.5 months. This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Special populations

Pediatrics (less than 18 years of age)

The pharmacokinetics of bedaquiline and its major metabolite *N*-monodesmethyl bedaquiline (M2) in 15 adolescent patients 14 years to less than 18 years of age with MDR-TB receiving 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 were comparable to those in adult patients with MDR-TB using the same dose regimen. There was no impact of body weight on bedaquiline pharmacokinetics in adolescent patients in trial C211 (38 to 75 kg), similar to what was observed in adults.

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

The pharmacokinetics of bedaquiline and its major metabolite M2 in 15 pediatric patients 5 years to less than 11 years of age (body weight: 14 to 36 kg) with MDR TB receiving 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 were comparable to those in adult patients with MDR-TB using the adult dose regimen.

Integrated population pharmacokinetic analysis (5 years to less than 18 years of age)

An integrated population pharmacokinetic analysis demonstrated that the bedaquiline exposure in patients 5 years to less than 18 years for the recommended weight-based dosing regimen (Table 1) is similar to adult patients.

Pediatric patients (less than 5 years of age)

The pharmacokinetics of SIRTURO™ in pediatric patients less than 5 years of age or weighing less than 15 kg have not been established.

Elderly (≥ 65 years of age)

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

In a population pharmacokinetic analysis of TB patients treated with SIRTURO™, age was not found to influence the pharmacokinetics of bedaquiline.

Renal impairment

SIRTURO™ has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is insignificant (< 0.001%).

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

Hepatic impairment

After single-dose administration of SIRTURO™ to 8 subjects with moderate hepatic impairment (Child Pugh B), exposure to bedaquiline and M2 (AUC_{672h}) was 19% lower compared to healthy subjects. No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population (see *Dosage and Administration*).

Other populations

Race

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

Gender

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

HIV Co-infection
There are limited data on the use of SIRTURO™ in HIV co-infected patients (see *Warnings and Precautions*).

5.3 NON-CLINICAL INFORMATION

Animal toxicology studies have been conducted with bedaquiline administration up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. The plasma bedaquiline exposure (AUC) in rats and dogs was similar to that observed in humans. Bedaquiline was associated with effects in target organs which included monocytic phagocytic system (MPS), skeletal muscle, liver, stomach, pancreas and heart muscle. All of these toxicities except effects on MPS were monitored clinically. In the MPS of all species, pigment laden and/or foamy macrophages were also seen in various tissues, consistent with phospholipidosis. The significance of phospholipidosis in humans is unknown. Most of the observed changes occurred after prolonged daily dosing and subsequent increases in plasma and tissue concentrations of the drug. After treatment cessation, all indications of toxicity exhibited at least partial recovery to good recovery.

Carcinogenicity and Mutagenicity

Bedaquiline was not carcinogenic in rats up to 20 mg/kg/day in males and 10 mg/kg/day in females. Compared to the exposures observed in subjects with MDR-TB in the bedaquiline Phase 2 trials, the exposures (AUC) in rats at the No Observed Adverse Effects Level (NOAEL) for carcinogenicity were similar in males and 2-fold higher in females for bedaquiline, and 3-fold higher in both males and females for M2.

In vitro and *in vivo* genotoxicity tests indicated that bedaquiline did not have any mutagenic or clastogenic effects.

Reproductive Toxicology and Fertility

Bedaquiline had no effects on fertility when evaluated in female rats. Three of 24 male rats treated with high bedaquiline doses failed to produce offspring in the fertility study. Normal spermatogenesis and a normal amount of spermatozoa in the epidydimides were noted in these animals. No structural abnormalities in the testes and epididymides were seen after up to 6 months of bedaquiline treatment. No relevant bedaquiline related effects on developmental toxicity parameters were observed in rats and rabbits. The corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. In the rat, no adverse effects were observed in a pre- and post-natal development study at maternal plasma exposure (AUC) similar to humans and exposure in the offspring 3-fold higher than in adult humans. There was no effect of maternal treatment with bedaquiline at any dose level on sexual maturation, behavioral development, mating performance, fertility or reproductive capacity of the F1 generation animals. Body weight decreases in pups were noted in high dose groups during the lactation period after exposure to bedaquiline via milk and were not a consequence of *in utero* exposure. Concentrations of bedaquiline in milk were 6- to 12-fold higher that the maximum concentration observed in maternal plasma.

6 PHARMACEUTICAL INFORMATION

6.1 List of Excipients

SIRTURO™ 20 mg

Colloidal anhydrous silica, Crospovidone, Hypromellose 2910 5 mPa.s, Polysorbate 20, Purified water (removed during processing), Silicified microcrystalline cellulose, Sodium stearyl fumarate

SIRTURO™ 100 mg

Colloidal anhydrous silica, Corn starch, Croscarmellose sodium, Hypromellose 2910 15 mPa.s, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Polysorbate 20, Purified water (removed during processing)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

See expiry date on the outer pack.

6.4 Storage Conditions

SIRTURO™ 20 mg

Keep out of the sight and reach of children.

Store in the original container in order to protect from light and moisture. Keep the container tightly closed. Do not remove desiccant.

SIRTURO™ 100 mg

Keep out of the sight and reach of children.

Store in the original container or package in order to protect from light.

6.5 Nature and Contents of Container

SIRTURO™ 20 mg

60 tablets packaged in an opaque white high density polyethylene (HDPE) bottle with child-resistant polypropylene (PP) closure with induction seal liner. Each bottle contains silica gel desiccant.

SIRTURO™ 100 mg

188 tablets packaged in a white HDPE bottle with child-resistant PP closure with induction seal liner.

Carton containing 4 push-through blister strips (containing 6 tablets per strip). Tablets are packaged in aluminium/aluminium foil blisters.

6.6 Instructions for Use and Handling

Not applicable.

6.7 Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MANUFACTURED BY

See outer carton.

RECIPHARM PHARMA SERVICES, BANGALORE, INDIA

MAH

BLOOMS PHARM LTD., SURULERE LAGOS.

DATE OF REVISION OF THE TEXT

02-March-2021 (based on CCDS dated 02 February 2021)